ALEUKEMIC MYELOSIS

CHRONIC NONLEUKEMIC MYELOSIS, AGNOGENIC MYELOID META-PLASIA, OSTEOSCLEROSIS, LEUKO-ERYTHROBLASTIC ANEMIA, AND SYNONYMOUS DESIGNATIONS *

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The existence of a disease closely related to, or a variant of, myelogenous leukemia has been known for many years. It presents features sufficiently distinct in certain respects to have resulted in its segregation from leukemia by numerous investigators. Thus, its exact relationship to leukemia has not been fully clarified. In this paper we present the evidence forming the basis for our interpretation that the disease is fundamentally leukemic, an interpretation generally implicit in the designation, aleukemic myelosis. The uncertainty in the classification of this disease has resulted in a diverse and confusing nomenclature, as illustrated in Table I.

The disease is characterized clinically by a slowly progressive splenomegaly occurring in persons of either sex, usually within or beyond the fifth decade of life. There may be little impairment in the general health for many years, following which generalized weakness, anorexia, weight loss, ill defined aches and pains, and discomfort, occasioned by the greatly enlarged spleen, frequently occur. The liver may enlarge. As a rule there is no significant involvement of the lymph nodes. The blood picture varies within relatively wide limits. There is usually an anemia of mild to moderate severity often associated with the presence of immature red blood cells. The white blood count may be elevated, at times to a degree suggestive of leukemia. Smears of peripheral blood may reveal immature myeloid cells. However, the degree of leukocytosis and the immaturity of the white blood cells, as a rule, are not typically leukemic and some cases have no leukemoid features.

Within the past 2 years we have had the opportunity of observing three cases of the disease. In one, only the spleen was available for

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pathologic study. Autopsy examination was performed in the other two cases. Repeated blood studies were performed in each case, although in case 3 observation of the blood by one of us was limited to a single examination.

TABLE I

Terminology Referable to:

A. Leukemia

Aleukemic myelosis [1-7]
Aleukemic leukemia [8*, 9†]
Pseudoleukemia [10-12]
Chronic nonleukemic myelosis [13-15]
Osteosclerotic leukemia [16]
Atypical myelosis [17]
Megakaryocytic myelosis [18]

B. Anemia

Leukanemia [19-21]
Myeloid splenic anemia [22]
Leuko-erythroblastic anemia,[23] leuko-erythroblastosis [24]
Osteosclerotic anemia [25]

C. Spleen and/or Liver

Splenomegaly with anemia and myelemia [26]
Myelophthisic splenomegaly [27]
Aleukemic hepatosplenic myelosis [28]
Agnogenic myeloid metaplasia of the spleen [29,30]
Myeloid megakaryocytic hepatosplenomegaly [31]
Splenomegaly with sclerosis of the bone marrow [32]
Splenomegaly with myeloid transformation [33]
Splenomegaly with anemia [34]
Myeloid splenomegaly without myelocythemia [35]

D. Bone Marrow

Myelofibrosis [36,37]
Myelosclerosis [9,38]
Osteosclerosis [5,6,15,18,39]

* Cases 1, 2, and 8.
† Cases 8, 9, and 10.

CASE I

Mrs. B. J., a white woman, 58 years old, was admitted to the Butler County Memorial Hospital, service of Dr. Carl Danielson, on January 26, 1944, complaining of loss of weight, anorexia, and vague abdominal pain of several months' duration. The onset of her illness had been gradual and the symptoms had become progressively more severe. The remainder of the history was not noteworthy. Physical examination revealed a poorly nourished, frail woman in no apparent discomfort. The physical findings were normal· except for a moderately firm, smooth spleen which extended to the level of the umbilicus. The red blood cells were 3,260,000 per cmm.; hemoglobin, 58 per cent; white blood cell count, 20,000 per cmm.; neutrophils (unclassified), 65 per cent; lymphocytes, 33 per cent; monocytes, 2 per cent. After a blood transfusion the erythrocytes rose to 3,640,000 per cmm., and the hemoglobin to 63 per cent. A second white blood cell count was 12,700 per cmm. On February 8, 1944, splenectomy was performed. The postoperative course, during which time she received 2,000 cc. of blood by transfusion, was uneventful. She was discharged on March 3, 1944.

Post-Mortem Findings

The spleen was uniformly enlarged. It weighed 1,000 gm. and measured 24 by 13 by 9 cm. The organ had a firm consistency and was reddish brown, mottled with small darker hemorrhagic areas. On section, the parenchyma bulged slightly and was dark red, firm, and rela-

tively bloodless. There were numerous small, slightly elevated, irregular, hemorrhagic, nodular areas generally less than 1 cm. in diameter (Fig. 1). The lymphoid follicles were indistinct. Beneath the capsule a sharply circumscribed nodule, 1.5 cm. in diameter, was noted. Its cut surface was pale yellow, solid, and irregularly hemorrhagic.

Microscopic Examination

Sections of the spleen revealed an extensive pleomorphic cellular infiltration which had caused wide separation and atrophy of the lymphoid follicles. Throughout the pulp were innumerable myeloid cells at various stages of maturity from myeloblasts to segmented polymorphonuclear leukocytes. The sinusoidal spaces contained similar cells in small numbers. Scattered mitotic figures were noted in the immature cells. The lining reticulo-endothelial cells were enlarged and in areas appeared to be in process of separating from the underlying reticulum. Large multinucleated giant cells of megakaryocytic type were noted in the sinusoidal spaces, frequently lying on the reticulum of the wall. They possessed an abundant acidophilic nongranular cytoplasm and dark nuclei, multiple or coarsely lobate. Smaller, poorly developed forms resembled stages of transition from the hyperplastic reticuloendothelial cells. In some areas nucleated red blood cells were relatively numerous. The nodules noted grossly were not encapsulated and consisted chiefly of tightly packed myeloid cells, including numerous giant cells (Fig. 2).

Postoperative blood studies are collected in Table II. A notable feature of the blood smears was the presence of giant platelets, frequently larger than the erythrocytes (Fig. 3). They were often hypochromatic and at times exhibited central vacuolization.

Additional laboratory studies revealed normal values for bleeding and clotting time, clot retraction, blood sugar, nonprotein nitrogen, serum phosphorus, and serum calcium. Sedimentation rate was 32 mm. in 1 hour; hematocrit, 32 per cent; hemolysis began at 0.48 and was complete at 0.34. The icterus index was 10 units; the reticulocyte count was 3.7 per cent. Serologic tests for syphilis were negative. Urine specimens were normal.

Roentgenograms of both femora revealed a normal texture.

At the present time, about 2 years following splenectomy, the patient is in poor health, having derived no apparent benefit from the operation. A recent radiologic examination revealed irregular areas of osteosclerosis involving the ribs, clavicles, and heads of the humeri. There has been no material change in her complaints, except for the occurrence of moderately severe epistaxis occurring at monthly intervals.

CASE 2

Mrs. A. B., a white housewife, 59 years old, was admitted to the Allegheny General Hospital, service of Dr. C. W. W. Elkin, on September 11, 1938, complaining of pain in the left upper abdominal quadrant and a palpable mass in that area which had been present, to the patient's knowledge, for 12 years. She also complained

TABLE II

Postoperative Studies of the Blood in Case 1

Date	2-14-44	2-19-44	2-20-44	2-21-44	2-22-44	2-23-44	2-26-44	4-6-44	5-11-44	3-28-45	1-30-46
Red blood cells (millions)	3.250	2.350	2.900	3.000	3.050	3.600	3.390	3.500	3.050	3.150	2.180
White blood cells	12,700	32,700	34,600	28,200	25,600	26,800	25,400	40,000	51,250	58,800	50,400
Hemoglobin in %; 14.5 gm. = 100%	55	46	52	54	56	69	62	58	52	58	47
Platelets	264,750	164,500	201,800	270,000	279,750	306,500					
Differential counts											
Segmented polymorphonuclear leukocytes	16	8	7		4		7	4	5	7	2
Rod-nuclears	42	29	52		40		58	33	23	20	39
Metamyelocytes	6	17	16		30		21	13	18	22	18
Myelocytes	12	11	7		15		4	9	20	11	9
Premyelocytes	5	1	1		0		0	0	2	3	9
Myeloblasts	0	0	0		0		0	6	10	8	8
Lymphocytes	18	34	15		10		10	29	20	18	8
Eosinophils	1	0	1		0		0	2	2	11	5
Monocytes	0	0	1		1		0	4	0	0	2
Normoblasts	6	76	49		14		3	19	10	0	41
Megaloblasts	1	2	0		0		0	0	0	0	0

of mild intermittent precordial pain and slight exertional dyspnea of long duration, and generalized "neuritic" pains. The remainder of the history was irrelevant.

Physical examination revealed a well nourished, well developed woman, not appearing ill. The temperature and pulse were normal. Blood pressure was 140/70 mm. Hg. There was a systolic murmur over the precordium. The spleen was considerably enlarged, extending slightly beyond the midline and below the level of the umbilicus. It had a firm consistency and a somewhat rounded edge. The lower border of the liver extended from 3 to 4 fingersbreadth below the costal border. It was smooth and firm. There was no palpable enlargement of the lymph nodes.

The patient would not submit to biopsy of the sternal marrow and was discharged after 9 days with the diagnosis undetermined.

Roentgenograms of the chest and abdomen were noncontributory. The electrocardiogram was normal except for left axis deviation.

Laboratory Findings. The red blood cells were 4,500,000 per cmm.; hemoglobin, 70 per cent (10.5 gm.); white blood cell counts were 8,500 and 8,800 per cmm.; differential count: segmented polymorphonuclear leukocytes, 51 per cent; nonsegmented neutrophilic leukocytes, 19 per cent, with occasional metamyelocytes representing the most immature cell type; eosinophils, 1 per cent; basophils, 4 per cent; lymphocytes, 24 per cent; monocytes, 1 per cent. The erythrocytes showed moderate anisocytosis, poikilocytosis, and occasional stippling; normoblasts were noted infrequently. The blood sugar and nonprotein nitrogen were normal. Serologic tests for syphilis were negative. The urine contained a faint trace of albumin and a few white blood cells.

Four and one-half years later, on March 4, 1943, the patient was admitted to the Presbyterian Hospital, service of Dr. C. W. Morton, with a severe infection of the upper respiratory tract. Physical findings were unchanged, except for a somewhat larger spleen.

Laboratory Findings. The red blood cells were 3,310,000 and 3,790,000 per cmm.; hemoglobin, 55 and 60 per cent; white blood cell count, 8,400 per cmm.; polymorphonuclear neutrophils, 44 per cent; lymphocytes, 48 per cent; monocytes, 8 per cent. She was discharged on March 9, 1943.

On February 12, 1945, 2 years later, she was readmitted to the Presbyterian Hospital complaining of weakness, weight loss, anorexia, nausea, vomiting, and vague abdominal distress. She appeared chronically ill. The spleen was massive and the liver was moderately enlarged. The physical findings were otherwise unaltered.

Laboratory Findings. The red blood cells were 2,480,000 per cmm.; hemoglobin, 40 per cent; several white blood cell counts varied between 5,400 and 16,300 per cmm. Average values for several differential blood counts were as follows: segmented neutrophilic leukocytes, 20.4 per cent; rod-nuclears, 30.5 per cent; metamyelocytes, 16.8 per cent; myelocytes, 8.6 per cent; eosinophils, 3.5 per cent; lymphocytes, 18.4 per cent; monocytes, 1.8 per cent; normoblasts, from 2 to 52 per 100 white blood cells; megaloblasts, 10 per 100 white blood cells in one smear.

Following a progressively downhill course with periods of intermittent fever and extreme weakness the patient died on March 14, 1945, 19 years after the splenic enlargement was first noted.

Post-Mortem Findings

Autopsy was performed 3 hours after death. External examination revealed nothing noteworthy. The lungs and heart were normal.

The spleen was enormously enlarged, extending beyond the midline and below the level of the umbilicus. It weighed 2,190 gm. and meas-

ured 30 by 18 by 8 cm. The capsule was irregularly thickened, but smooth. The organ was a mottled bluish purple and moderately firm. On section a dark red, fleshy parenchyma studded with small, poorly defined nodules was noted. The nodules were distinguished from the adjacent pulp by a firmer texture and slight elevation. A few were pale. There was no apparent encapsulation of the nodules and their borders merged imperceptibly into the adjacent pulp tissue. The lymphoid follicles were not grossly evident. Small areas of scarring were noted, but no infarcts.

The liver was enlarged and weighed 2,425 gm. It was firm and of a uniform light tan color. The lower border of the right lobe was somewhat rounded. On section the parenchyma was pale and free of localized lesions. There was no apparent disturbance in the portal architecture. The lymph nodes of the thorax or abdomen were not altered in size or appearance. The bone marrow of vertebrae, ribs, sternum, ilium, and neck of femur appeared cellular and somewhat paler than is normal.

No other significant gross abnormalities were evident.

Microscopic Examination

Spleen. An abundant myeloid tissue replaced much of the splenic pulp. The fibrous septa and lymphoid follicles were widely separated, the latter being small and compressed, but distinct. The intensity of the myeloid reaction varied. It occurred in a diffuse manner, but in some areas there were circumscribed nodular masses of closely packed myeloid cells which were not encapsulated. Numerous large, irregular giant cells of megakaryocytic type were conspicuous, generally located within the sinuses (Fig. 4). The cytoplasm of these cells was abundant, homogeneous, hyalin-like, nongranular, and intensely acidophilic. The nuclei were large, often huge, and generally oval or coarsely lobular, lightly basophilic and vesicular. Pyknotic forms were encountered at times. The majority of these cells were multinucleated, often containing a dozen or more nuclei. Present within the sinusoids, in large numbers, were irregular clusters of immature myeloid cells, myeloblasts predominating. The latter had a lightly basophilic, slightly granular cytoplasm. The nuclei were large, round, and vesicular with a prominent nuclear membrane enclosing a stippled chromatin structure. Prominent nucleoli and mitotic figures were frequent. More mature forms, exhibiting cytoplasmic granulations, both neutrophilic and eosinophilic, were in evidence. Polymorphonuclear leukocytes, lymphocytes, and scattered erythrocytes were present, in smaller numbers, in the sinusoids. In the interstitial tissue there were many erythrocytes, lympho-

cytes, and numerous relatively mature myeloid cells. Compressed masses of lymphoid tissue could be identified, representing remnants of the lymphoid follicles. Normal appearing reticulo-endothelial cells were occasionally encountered along the sinusoids. Many resembled developmental stages of transition into myeloblasts or megakaryocytes (Figs. 5 and 6). Their position upon the wall of the sinus was suggestive of their local origin from reticulo-endothelial cells. No erythropoietic activity was in evidence. Smears of fresh pulp made at the autopsy and stained with peroxydase and Wright's stain revealed no normoblasts or other erythropoietic cells. In addition to lymphoid cells and erythrocytes there were numerous myeloid cells, the majority containing scattered oxydase-positive granules.

Lymph Node. A peribronchial lymph node revealed extensive anthracotic pigmentation and fibrosis. Large, irregular, multinucleated giant cells resembling megakaryocytes were infrequent along the sinusoidal walls. There was no additional evidence of hematopoiesis.

Bone Marrow. Sections from the bodies of the lumbar vertebrae, sternum, ribs, ilium, and femur were examined. In all areas there was an intense pleomorphic myeloid hyperplasia which had replaced the marrow fat (Fig. 7). There were small, widely scattered areas of fibrosis which did not significantly alter the appearance of intense hyperplasia. Prominent throughout all areas were megakaryocytes, increased in number above normal. Generally they were located in irregular sinusoidal spaces. Immature myeloid tissue, in cellular nests, frequently distended the vascular spaces. The interstitial tissue was composed of closely packed myeloid cells in various stages of development, for the most part moderately well differentiated. In some areas eosinophilic myelocytes and metamyelocytes were unusually numerous. Mitotic figures were frequently noted in the immature cells. There was an obvious reduction, and in most areas complete suppression, of erythropoietic activity. Small clusters of normoblasts and megaloblasts were encountered occasionally.

Liver. Sections of the liver revealed a moderately advanced passive congestion. The portal areas showed no infiltration with myeloid cells. The lobular structure was well maintained. A moderately heavy, diffuse, myeloid involvement of the sinusoidal spaces was noted (Fig. 8). Elongated giant cells, usually multinucleated, were scattered in small numbers within the sinuses, generally lying near the sinus wall in endothelial fashion (Fig. 9). Myeloid cells in various stages of development were prominent in these areas.

Sections of thyroid, lungs, heart, gastrointestinal tract, kidneys, adrenals, pancreas, uterus, and tubes showed no myeloid involvement.

A. W., a white male, 73 years old, was admitted to the Western Pennsylvania Hospital, service of Dr. Frank A. Evans, on October 26, 1939, complaining of weakness, anorexia, weight loss, and mild dyspnea. The symptoms had been most pronounced for a month prior to admission, but their onset had been insidious and rather indefinite. In the preceding 3 years there had been a weight loss of 100 lbs.

Physical examination revealed a well developed, fairly well nourished patient in no acute distress. The skin and mucous membranes were pale. There was slight icteric discoloration of the skin and sclerae. There was no atrophy of the glossal papillae. No enlargement of the superficial lymph nodes was noted. The lungs were clear. There was a harsh systolic murmur noted at the apex and base of the heart. There was no apparent cardiac enlargement. Blood pressure was 130/85 mm. Hg. There were no abnormal findings referable to the abdomen. The spleen was not palpated. There was diminished vibratory perception in the extremities. No additional neurologic abnormalities were noted, other than partial deafness. Preliminary blood studies were highly suggestive of pernicious anemia, and intense parenteral therapy with concentrated liver extract was instituted. The anemia responded well to liver therapy supported by two transfusions of whole blood. The patient was discharged, considerably improved, on November 18, 1939.

Laboratory Findings. Examination of the urine and feces revealed nothing noteworthy. On admission the red blood cell count was 950,000 per cmm.; hemoglobin, 15 per cent; white blood cell count, 1,600 per cmm. The erythrocytes showed considerable anisocytosis and poikilocytosis. Nucleated red blood cells were noted. Differential examination of the leukocytes revealed: neutrophils, 46 per cent; small lymphocytes, 46 per cent; large lymphocytes, 5 per cent; monocytes, 3 per cent. The icteric index was 20. There was total absence of free hydrochloric acid in the gastric juice on two occasions. There was a progressive rise in the red blood cell count to 3,500,000 per cmm. at the time of discharge. The hemoglobin had risen to 71 per cent. The reticulocytes rose rapidly from an initial 0.2 per cent to a maximum of 12 per cent 13 days after the onset of liver therapy. There was a persistent leukopenia, the white blood cell count ranging between 1,600 and 4,600 per cmm., usually between 2,000 and 3,000 per cmm. There was no significant change in the differential percentages, and immature granulocytic forms were not noted. Normoblasts were recorded repeatedly.

Six years later, on August 30, 1945, the patient was admitted to the Presbyterian Hospital, service of Dr. W. A. Bradshaw. He complained of weakness and loss of weight, present intermittently since 1939. The weakness had diminished during periods of liver therapy until 3 months prior to admission.

Laboratory Findings. The red blood cell count was 1,780,000 per cmm.; hemoglobin, 37 per cent; white blood cell count, 10,800 per cmm. Differential count of 200 cells revealed: segmented neutrophils, 69.5 per cent; rod-nuclears, 14.5 per cent; metamyelocytes, 3.5 per cent; myelocytes, 3 per cent; lymphocytes, 7.5 per cent; monocytes, 1.5 per cent; basophils, 0.5 per cent; 16 normoblasts and 3 megaloblasts were noted. Gastric analysis revealed no free hydrochloric acid. Other examinations yielded nothing noteworthy.

Physical findings were essentially those of his former admission, and his general condition was poor. He was afebrile until the third day when he suffered a shaking chill with a rise of temperature to 105° F. He continued febrile and died 5 days after admission.

Post-Mortem Findings

Autopsy was performed 1½ hours after death. There were no significant external abnormalities. The superficial lymph nodes were not enlarged. The lungs showed congestion and irregular areas of broncho-

pneumonic consolidation in both lower lobes. There was moderate arteriosclerotic thickening of the leaflets of the mitral and aortic valves. There were 1,500 cc. of clear ascitic fluid in the peritoneal cavity. The surface of the liver was finely granular and mottled brown and yellow. It weighed 2,280 gm. It cut with a fibrous resistance. Its cut surface was delicately nodular and the lobular structure was not clearly evident. There was a delicate fibrosis throughout, the pale fibrous stroma contrasting with the brown parenchyma.

The spleen was considerably enlarged but did not extend below the lower costal border. It weighed 1,110 gm. and measured 20 by 16 by 6 cm. Its upper surface was densely adherent to the peritoneal surface of the diaphragm. The cut surface was uniform in appearance throughout; it was reddish pink, fleshy, and moderately firm. The lymphoid follicles were small and indistinct. Little blood escaped from the cut surface.

The paravertebral lymph nodes were moderately enlarged, measuring up to 4 cm. in diameter. On section the parenchyma was pale, glistening, translucent, and fleshy. The bone marrow of the vertebral bodies and sternum was red and grossly normal in appearance.

There were no significant alterations noted in the other abdominal viscera.

Microscopic Examination

Spleen. Throughout the splenic pulp there were large numbers of myeloid cells in various stages of development. Numerous myeloblasts were encountered in the sinusoids as well as throughout the interstitial tissue. A few mitotic figures were noted in them. Giant cells of megakaryocytic type, frequently multinucleated, were occasionally noted. They were generally located along the sinusoidal walls in endothelial fashion. The reticulo-endothelial cells were prominent and stages of transition into giant cells were encountered. There was no significant increase in the fibrous stroma. The septa and lymphoid follicles were widely separated. The follicles were frequently atrophic and irregularly infiltrated with myeloid cells (Fig. 10). Clusters of cells with small, compact, hyperchromatic nuclei and oxyphilic cytoplasm were noted infrequently; they were regarded as normoblasts.

Lymph Nodes. Sections of paravertebral lymph nodes revealed irregular myeloid transformation of the parenchyma, of slight extent in some nodes, of considerable extent in others. Myeloblasts, myelocytes, neutrophilic leukocytes, and intermediary forms resulted in a notable pleomorphism, accentuated by numerous giant cells within the sinusoidal spaces (Fig. 11). Morphologically, the latter cells were identical to those of spleen and liver but were much more numerous

than in those organs. The myelosis had replaced much of the lymphoid pulp, had distorted the cords and sinusoids, and compressed and infiltrated some of the lymphoid follicles. In the nodes exhibiting the most intense myelosis, however, subcapsular follicles of normal size and appearance were evident.

Bone Marrow. The marrow of the vertebrae and sternum was uniform in appearance. There was considerable reduction of the marrow fat resulting from intense myeloid proliferation (Fig. 12). Various types of myeloid cells were represented. Mitotic figures were occasionally noted in the more immature cells. Prominent in the reaction were numerous megakaryocytes, cytologically normal. Only small scattered foci of erythropoiesis were identified. There was no significant fibrosis of the marrow and the bony lamellae were normal in size and structure.

Liver. There was slight to moderate disturbance in the portal structure of the liver, and small rounded nodules of hepatic parenchyma, without a central vein and surrounded by thickened portal stroma, were frequently noted. The appearance was that of portal cirrhosis of only moderate extent. Irregularly distributed throughout the sinusoidal spaces were myeloid cells in various stages of development. There were many giant cells, frequently having large lobate or multiple nuclei, lying along the walls of the sinusoids. The Kupffer cells were prominent and double-nucleated forms were noted. Frequently the portal stroma was infiltrated with young myeloid cells (Fig. 13). No giant cells were noted in these areas. The hepatic cord cells generally appeared normal, but in some areas contained considerable fat.

Sections of thyroid, heart, lungs, gastrointestinal tract, kidneys, adrenals, pancreas, bladder, and prostate showed no myeloid reaction. No pathologic features suggestive of pernicious anemia were noted.

MORPHOLOGIC FEATURES

Inasmuch as cases such as we have reported have been interpreted by numerous investigators as representing a disease other than leukemia, it is necessary (1) to present the evidence for our interpretation as leukemia and (2) to invalidate the criteria which have served to differentiate the disease from leukemia. Although we shall refer to the disease under discussion as aleukemic myelosis, it must be emphasized that comments referable to this disease are generally applicable to cases described in the literature under the terminology of Table I.

In the final analysis, the pathologic features offer the strongest basis upon which to form conclusions regarding the nature of a disease process. The clinical and hematologic findings are a reflection of the basic tissue reaction.

The gross features of typical myelogenous leukemia are the result of myeloid proliferation, characteristically of bone marrow, liver, spleen, and, to a variable extent, in the lymph nodes. In aleukemic myelosis grossly similar changes are encountered with the qualification that the bone marrow of some cases may be hypoplastic or sclerotic.

Spleen

The spleen was considerably enlarged in all three cases. In two, nodules were visible over the cut surface. The lymphoid follicles were not distinct. Fibrosis was not a prominent feature. No infarcts were noted.

Jackson, Parker, and Lemon[29] considered the absence of splenic infarcts, so common in myelogenous leukemia, as a feature differentiating "agnogenic myeloid metaplasia" from the former disease. Such a criterion could hardly be considered as fundamental inasmuch as infarcts are variable lesions subject to conditions affecting the vascular supply. In a study of the spleen in 27 cases of chronic myelogenous leukemia, Krumbhaar and Stengel [40] recorded infarcts in only 9. Conversely, Churg and Wachstein [15] described infarcts in the spleen of a case of "chronic nonleukemic myelosis." In a case of "leuko-erythroblastic anemia with myelosclerosis," Vaughan and Harrison [88] noted a large infarct.

Microscopically, the pulp was largely converted into myeloid tissue in which all intermediary stages of development of the myeloid cells from myeloblasts to segmented polymorphonuclear leukocytes were recognizable. The diffuse myelosis and mitotic figures were impressively reminiscent of a genuine leukemic reaction. The myelosis had resulted in wide separation of the lymphoid follicles which, as a rule, were atrophic.

Generally, the lymphoid follicles of the spleen in myelogenous leukemia are destroyed by the exuberant myeloid proliferation. Their retention in aleukemic myelosis has served to differentiate it from leukemia. Obviously, the disappearance of the follicles is an atrophic and replacement phenomenon and entirely subject to the extent of the myelosis. That there is any fundamental distinction between incomplete and total myeloid conversion of the splenic parenchyma is doubtful. In the spleens of all three of our cases there was evidence of destruction of some of the follicles, remnants of which surrounded the central arteriole and were compressed by the surrounding myeloid tissue. Although the follicles are destroyed in most cases of leukemic infiltration of the spleen, occasionally in all types of leukemia they are preserved.[40] Callender's [41] Figure 3 depicts a histologically typical lymphoid follicle in the spleen from a case of myelogenous leukemia.

He observed that the myeloid proliferation involved the red pulp, between the lymphoid follicles.

In all of our cases giant cells of megakaryocytic type were noted. In two cases these cells were the elements chiefly responsible for the gross nodulation. Such nodules have been described previously.[4,18,31,32,33,42] Megakaryocytes frequently have been noted in the spleen in myelogenous leukemia.[40,43-46] It does not seem that their presence in excessive numbers in aleukemic myelosis constitutes a valid justification for segregating this disease from leukemia. They represent only one element of a pleomorphic myeloid cellularity. Furthermore, the exaggerated megakaryocytic proliferation is an inconstant feature of aleukemic myelosis. Some cases may exhibit minimal megakaryocytic metaplasia to a degree commonly observed in myelogenous leukemia, as exemplified by case 3.

The significance of the giant cells has been a subject of controversy, as to their relationship with megakaryocytes. The majority of observers regard the cells as megakaryocytes, a view to which we subscribe. Minor alterations in nuclear and cytoplasmic structure, staining reactions, cytoplasmic granulations, etc., in which they differ from the megakaryocytes of normal bone marrow,[42] would scarcely outweigh the fact that the splenic reaction is incontrovertibly an extra-osseous myelosis, and the only giant cells of myeloid tissue are megakaryocytes. Furthermore, minor morphologic variations from the megakaryocytes of normal marrow can be expected if the neoplastic concept of leukemia is accepted.

The alteration in the blood platelets in case 1 permits interesting speculation when correlated with the abnormal megakaryocytic reaction of the spleen. The megakaryocyte is the parent cell of the platelet.[47] One is tempted to associate the abnormal platelets with the abnormal splenic giant cells, as did Carpenter and Flory,[14] a relationship in no manner established in our case. Morphologic alterations in the blood platelets are commonly encountered in leukemia[48] and less frequently in other diseases. Abnormal platelets similar to those seen in case 1 have been described also by Rosenthal and Erf,[37] and Downey and Nordland.[31]

Liver

The gross appearance of the liver in our cases was not particularly striking. Myeloid infiltration was not grossly evident. In case 3 early portal cirrhosis had caused delicate nodulation. Microscopically, the hepatic sinusoids contained myeloid cells in various stages of development, the immature forms predominating. Giant cells presenting megakaryocytic characteristics were numerous. They appeared to take

origin from the Kupffer cells, an observation supported by the presence of transitional stages of development.

The reaction of the liver in myelogeneous leukemia consists of diffuse myeloid infiltration generally involving both the sinusoidal spaces and the portal areas. Giant cells of megakaryocytic type are not unusual. Aleukemic myelosis presents a myeloid infiltration different from typical leukemia in only one significant feature in many of the recorded cases, *i.e.*, absence of portal infiltrations. Such infiltrations were observed in case 3 and serve as one feature, among others, linking the disease with the more typical forms of myelogenous leukemia.

Lymph Nodes

In cases 1 and 2 there was no clinical evidence of lymph node involvement, which was confirmed at autopsy in the latter case. The paravertebral lymph nodes of case 3 were only moderately enlarged. The microscopic picture was one of diffuse myeloid infiltration of the pulp similar to that of the spleen. Such a state of myelosis of the lymph nodes is a common finding in myelogenous leukemia.[44,45,49-51]

Bone Marrow

Under conditions of the average post-mortem examination it is not possible to examine the skeleton thoroughly, and routine procedures generally constitute removal, for microscopic examination, of a portion of femur, vertebral body, sternum or rib, rarely all. That the examination of a single region accurately reveals the general state of the entire hematopoietic marrow is subject to question. Evidence indicates that such uniformity in the marrow cannot always be expected.[2,18,44,52,53] Of interest is Mallory's[54] observation of a case of leukemia, proved by biopsy of bone marrow, which subsequently developed a totally aplastic marrow.

In the field of clinical medicine implicit confidence is frequently placed upon a differential count of cells aspirated from sternal marrow, based upon the belief that comparatively few cells from the sternum reflect the general state of the hematopoietic marrow. This confidence is unshaken by the technical difficulties involved and strengthened by the knowledge that in many cases the procedure has been specifically diagnostic.

The sections of bone marrow from our two autopsy cases were considered to be sufficiently representative to reflect the true state of this tissue. Technically suitable preparation of marrow were available from three or more areas in each case. The reaction in both cases was that of intense myeloid hyperplasia which had resulted in a replace-

ment of much of the marrow fat. Myeloid cells in all stages of development were identified. Moderately frequent mitotic figures were noted in the more immature cells. In both cases megakaryocytes were numerous. The cellular pleomorphism and residual fat content differed from the usual picture of myelogenous leukemia; on the other hand, the intense cellularity, general state of cellular immaturity, the mitotic figures, and the suppression of erythropoietic activity were features to be expected in a leukemic marrow. The diminution of the erythropoietic tissue may be related to the presence of the immature erythrocytes noted in the circulating blood of both cases.

The striking similarity of the clinical, hematologic, and general pathologic features of numerous reported cases of aleukemic myelosis, differing only in respect to the bone marrow, has led to the belief held by many observers, including ourselves, that the marrow reactions are variants within one and the same disease. Jackson, Parker, and Lemon,[29] in presenting 10 cases of "agnogenic myeloid metaplasia," reported on the bone marrow findings as follows: normal marrow, 1 case; hyperplastic marrow, 1 case; aplastic marrow, 1 case; fibrosis of marrow (myelofibrosis), 5 cases; osteosclerosis, 1 case; and 1 case, unknown. "Hyperplastic foci of leukopoiesis" [36] in an otherwise fibrous marrow render interpretation particularly difficult in respect to the existence of hyperplasia or sclerosis.

Osteosclerosis of the type under discussion (excluding the Albers-Schönberg type) depends upon a thickening of the bony lamellae of the spongiosa by deposition of new bone at the periphery. From the numerous descriptions in the literature one gains the impression that the lamellar thickening is always associated with fibrosis of the adjacent marrow and is a manifestation of osseous metaplasia of the fibrous stroma. Conceivably, myelofibrosis and osteosclerosis may represent different stages of the same fundamental process. This interpretation has been expressed by others.[11,12,55]

Osteosclerosis cannot be regarded as a specific entity. It is a reactive lesion of bone marrow resulting from several possible stimuli,[18,56-58] such as secondary carcinoma of osteoplastic type, polycythemia vera, and exogenous toxins, as well as the myelosis of leukemia. Although it is generally recognized that fibrosis of the marrow may occur in myelogenous leukemia, one of the strongest of the criteria serving to differentiate aleukemic myelosis from leukemia has been the presence, in some cases, of osteosclerosis. In view of the intimate and probable causal relationship between myelofibrosis and osteosclerosis, the validity of this criterion is subject to question. However, until the finer structure of the bones has been more extensively studied, the signifi-

cance of osteosclerosis remains uncertain. The occurrence of osteo-
-clerosis in both leukemic and aleukemic myelosis has been reported
many times.[11,12,52*,58,58-61]

In the review of the bone marrow of 97 cases of leukemia by Churg
and Wachstein,[15] 6 cases were found to show myelofibrosis. One case
(case 4) of osteosclerosis was discovered and a revision of diagnosis to
a nonleukemic entity followed. The white blood cell count had been
as high as 125,000 per cmm., and 10 to 20 per cent myelocytes and 8
to 11 per cent myeloblasts were noted in the blood smears. The liver,
spleen, and lymph nodes showed widespread myelosis, and myeloid
infiltrations of epicardium, lungs, and kidneys were observed. If 6
cases of leukemia in that series could progress to a stage of myelofibro-
sis, why might not one case progress to osteosclerosis?

Thus, extreme diversity of the bone marrow may exist in aleukemic
myelosis. The transition of normal marrow to either a hyperplastic or
hypoplastic type and, in the latter event, to atrophy and fibrosis is
readily conceivable. Thus, the diversified alterations of the marrow
can be traced, step by step, from one extreme to the other. One ex-
treme is the massive proliferation of typical leukemia; the opposite
extreme is myelofibrosis and osteosclerosis.

In view of the fact that most of the reported cases of osteosclerosis
have been associated with aleukemic blood, it would seem that a causal
relationship may exist between the two. The diminution in the myeloid
tissue of the bone marrow coincident with the development of osteo-
sclerosis obviously results in a diminished supply of leukocytes to the
blood from this source. The extra-osseous myeloid foci may not con-
tribute immature cells to the blood with the same facility possessed by
active bone marrow. Still other unknown factors, however, are respon-
sible for the aleukemic state of the blood inasmuch as cases such as we
have reported are aleukemic and yet associated with a hyperplastic,
not sclerotic, bone marrow.

Interpretation as a Compensatory Mechanism

In many cases presenting evidence of deficient hematopoietic activ-
ity of the bone marrow, the extra-osseous myelosis has been regarded
as a compensatory phenomenon.[5,6,12,25,27,32,37,39,62] Such a view seems
entirely logical but, upon further analysis, several factors weaken this
concept. In the great majority of the recorded cases the cellular re-
action which resulted in massive enlargement of the spleen was pre-
dominantly leukopoietic. It is exceptional to encounter cases in which

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* The lesion of the bone marrow of this case was designated "ossifying osteomyelitis"
which is strongly presumptive of osteosclerosis.

erythropoiesis has been of any significant extent. A similar situation exists in reference to liver and lymph nodes. It would seem that if extra-osseous hematopoiesis were compensatory to failure of the bone marrow, erythropoietic activity would be a prominent feature of the reaction. Much more severe and persistent anemias, of other types, are not productive of the massive extramedullary hematopoiesis found in aleukemic myelosis.

At times the interpretation of deficient function of the bone marrow has been based entirely upon an unjustifiable inference. Ballin and Morse,[27] under the title "Myelophthisic Splenomegaly," reported two cases which we consider identical with ours. The pathologic study was limited to the surgically removed spleens and their interpretation that the splenic reaction was compensatory to bone marrow failure was not supported by any recorded observations of the bone marrow. The visceral myelosis of our cases cannot be regarded as compensatory inasmuch as the bone marrow was overactive. In all other essential respects our cases appear identical with cases having hypoplastic or sclerotic bone marrow. Thus, it would seem that there is no scientific basis for the assumption that the visceral myelosis of this disease is of compensatory nature.

Visceral Infiltrations

The absence of leukemic infiltration in viscera other than the spleen, liver, and lymph nodes in aleukemic myelosis has been a factor in the nonleukemic interpretation. In myelogenous leukemia such infiltrations are variable and inconstant. In an analysis of 123 cases of leukemia by Kirshbaum and Preuss,[51] the kidney was found to be the organ most commonly involved by leukemic infiltrations, excluding spleen, liver, and lymph nodes. In their series, however, the kidney showed no involvement in over one-third of the cases. Thus, the occurrence of visceral infiltrations would appear to be a totally unreliable criterion by which to differentiate aleukemic myelosis from leukemia, and an explanation for their absence will be offered subsequently.

HEMATOLOGIC FEATURES

That the blood picture in myelogenous leukemia is subject to considerable variability is well known, but the extent of the variability possible in any individual case is not entirely clear. The designation aleukemic frequently is applied to cases of leukemia in which the total white cell count of the circulating blood is within normal limits, although examination of a stained blood smear would reveal immature cells. Such observations are not rare, occurring either at one time or another in the natural course of the disease or as a result of therapy.

We consider it advisable to apply the term aleukemic myelosis to cases of myelogenous leukemia which are aleukemic in respect to both the differential count and the total leukocyte count. The basic leukemic nature of such cases is often unrecognized.

It has been questioned whether cases of myelogenous leukemia exist in which adequate repeated studies of stained blood smears by a qualified observer fail to reveal the leukemic proliferation which exists in the myeloid tissue of the body.[63] Since it is generally accepted that there are cases of myelogenous leukemia in which there is relatively slight alteration in the blood picture, the assumption that cases do not exist without any characteristic alteration of the white blood cells seems overly dogmatic.

Of interest are the blood studies of our three cases, two of which are presented with the implication that genuinely and permanently aleukemic forms of the disease do exist. In case 1, the preoperative blood examinations gave no evidence of a leukemic process. The postoperative studies at first merely aroused a suspicion, but a frankly leukemic picture subsequently developed. This was of major importance in the reversal of our original nonleukemic interpretation of the splenic reaction. In cases 2 and 3, adequate blood examinations over a period of several years failed to establish the diagnosis of leukemia.

Perhaps the most important factors leading to a nonleukemic interpretation of aleukemic myelosis have been the normal or only moderately elevated number of leukocytes in the blood, and their state of relative maturity. Such factors, in themselves, do not exclude leukemia. In reference to the total number of the white blood cells, it is universally accepted that myelogenous leukemia may exist without a numerical increase.[64] In 5 of 53 cases of myelogenous leukemia reported by Kirshbaum and Preuss [51] the total white count fell to less than 4,000 per cmm. In reference to cellular maturity, we have encountered cases of chronic myelogenous leukemia in which blast forms were not demonstrable, myelocytes being the least mature cell type present. Such cases are not unusual.[50] When depressed total count and cellular maturity are combined, the leukemic nature may not be recognized.

It is possible that many of the mature leukocytes of the circulating blood in cases such as ours are actually well differentiated leukemic cells, differentiated to such a degree that their leukemic nature cannot be recognized morphologically. Myelogenous leukemia of highly differentiated character may produce structural abnormalities only in the parent myeloid tissue and individual cellular elements of such growth, the circulating leukocytes, may be cytologically normal or negligibly

altered. Somewhat analogous are the individual neoplastic cells of a well differentiated adenocarcinoma, the diagnosis of which may be dependent entirely upon atypical organoid structure rather than upon morphologic alteration of individual tumor cells.

Much attention has been centered upon the presence of immature cells of the erythrocytic series. The presence of these, associated with anemia and immature granulocytic forms, has led to the designation "leuko-erythroblastic anemia," [23] a descriptive term of hematologic significance without pathologic implication. It is pertinent to emphasize that young erythrocytic cells occur almost constantly in the circulating blood of cases typically leukemic,[1,31,41,45,50] so their presence in aleukemic myelosis does not serve to differentiate it from leukemia. When a blood smear is flooded with immature myelogenous cells the nucleated red cells are much less conspicuous than they are in an aleukemic blood. The immature granulocytic cells in the blood of many cases of "leuko-erythroblastic" anemia (Vaughan type[23]), regardless of their number or relative maturity, are a manifestation of the underlying myeloid proliferation which we regard as leukemic. The state of the peripheral blood is not necessarily an indication of the condition of the somatic myeloid tissues and such blood pictures cannot exclude an underlying leukemic process. To characterize a disease as an entity based upon the blood picture and to misconstrue the significance of the underlying pathologic process leads to interpretive and nosologic confusion.

In many reported cases the authors' interpretations of the immature myeloid cells of the blood are not entirely clear. Thus, Downey, Palmer, and Powell,[17] in recording the differential blood count in a case of "atypical myelosis," did not include those cells in their differential percentages which, under "remarks," they designated as "many myeloblasts." Throughout the literature of this disease one encounters strikingly high percentages of immature myeloid cells in the blood, often associated with considerable elevation in the total white count. In Table III are several examples. The list could be extended considerably.

All of the cases included in Table III were presented by the authors, either by statement or implication, as examples of a disease distinct from leukemia. In the literature of this disorder the highest total count that we have encountered in cases presented by the author as representing a disease other than leukemia was 227,000 (Rosenthal and Erf,[37] case 14). In this case 42 per cent of the leukocytes were myelocytes. The authors excluded leukemia because of fibrosis of the bone marrow. In view of the not infrequent occurrence of myelofibrosis in leukemia,[15] one is justified in questioning this interpretation.

TABLE III

Total and Differential White Blood Cell Counts in Cases Considered by the Respective Authors as Examples of Diseases Differing from Leukemia

Author	Total white blood cells	Myelocytes (per cent)	Premyelocytes (per cent)	Myeloblasts (per cent)	Additional data (per cent)
Rosenthal and Erf[37] (case 6)	124,000	10		3	
Jordan and Scott[39]	32,000	20	25		Basophils 6
Vaughan and Harrison[38]	49,000	3		9	Basophils 7 Eosinophils 21
Hickling[18] (case 7)	60,000	20 (and blasts)			
Reich and Rumsey[30] (case 5)	86,000	20		6	
Carpenter and Flory[14]	86,300	11		8	
Downey and Nordland[31]	79,700	1	10	24	

(When more than one observation was recorded, the figures in the above table represent the highest.)

CLINICAL FEATURES

The prolonged clinical course of many cases of aleukemic myelosis, as exemplified by our second case with a history of splenomegaly for 19 years, has been advanced as a feature differentiating the disorder from leukemia. Admittedly, such a survival period in leukemia is most unusual but scarcely serves as a scientific basis for its exclusion. Forkner[45] observed a patient with chronic myelogenous leukemia for 18 years. Survival for a period of 25 years has been reported.[65]

Prolonged survival periods in aleukemic myelosis are unusual and the survival time of many cases is fully equivalent to that of the usual case of myelogenous leukemia. Körner[66] reported a case, which was indistinguishable pathologically from aleukemic myelosis, with an accelerated clinical course and a rapidly fatal outcome. Zypkin[10] described acute myelogenous leukemia, aleukemic in reference to the blood smear, many years ago. Baldridge and

Fowler [7] observed a more rapidly fatal course in the aleukemic type of myelosis as compared with the leukemic forms. Thus, it would seem that there is great variability in the duration of the disease, just as there is in typical myelogenous leukemia.

It has been noted that the majority of patients with aleukemic myelosis, treated by irradiation, do not show the beneficial response characteristic of myelogenous leukemia and many have apparently suffered from such therapy. The beneficial response in leukemia is generally reflected by a drop in the total white count, and it is a well known observation that radiotherapy in leukemia is hazardous when the total white count of the blood drops below a level somewhat greater than the normal. Thus, one might predict an indifferent or unfavorable response in cases of leukemia with an initial normal or only slightly elevated total white count. That all cases may not exhibit such an unfavorable response is indicated by the observation of Dameshek [57] of a case presenting all the diagnostic criteria of "agnogenic myeloid metaplasia" in which the patient improved following radiotherapy. Benefit from radiotherapy has been reported by others [3,6,24,28,67] The response to radiotherapy does not serve as a valid criterion for distinguishing the disorder from leukemia.

A large percentage of the recorded cases in which the patients were subjected to splenectomy terminated fatally within a short period of time following the operation. Patients surviving for several years following splenectomy have been observed. As a practical consideration in the therapy of such cases the danger of splenectomy is evident, but as a factor differentiating the disease from myelogenous leukemia it is valueless. No beneficial effect can be expected from splenectomy in myelogenous leukemia.

INTERMEDIARY FORMS

To establish the leukemic nature of the disease under discussion, certain cases are presented which constitute intermediary forms linking this disorder with typical myelogenous leukemia. Case 3 serves as one example in which portal infiltrations of the liver were observed. Levy's [2] case, reported as leukemia, showed myelosis of the liver and spleen with retention of the lymphoid follicles, leukemic infiltrations of the kidneys, and hyperplasia of the bone marrow. The total white blood cell count had been normal. Mettier and Rusk [36] reported a case of leukemia (case 1) with a normal total white blood cell count. The spleen, removed surgically, showed myeloid metaplasia with lymphoid follicles normal in size and number. The white blood cell count exceeded 25,000 per cmm. postoperatively, with 54 per cent myelocytes

in the blood smear. At autopsy the bone marrow was grossly osteo-
sclerotic, microscopically fibrotic. The lymph nodes showed extensive
myelosis. Case 2, presented as leukemia by the same authors, showed
clinical features of chronic myelogenous leukemia. Pathologically, the
essential structure of the spleen was preserved. There was no portal in-
filtration of the liver but numerous myeloid cells were present in the
sinuses. Small myeloid infiltrations of the testes were noted. The
bones showed myelofibrosis. A case reported by Krumbhaar and Sten-
gel [40] as chronic myelogenous leukemia of mild myelopoietic ability
showed no significant elevation of the white blood cell count but many
immature myeloid cells in the blood smear. The bone marrow was
hyperplastic. The liver showed no myeloid reaction. Myelocytic in-
filtration of the splenic pulp had not destroyed the lymph follicles.
Körner's [66] case of myelogenous leukemia had a normal total white
blood cell count and immature myeloid cells in the blood smear. Death
occurred a few weeks after the onset of symptoms. Autopsy showed
myelosis of spleen, liver, and lymph nodes with numerous giant cells of
megakaryocytic type. The bone marrow was hyperplastic. Hickling's[18]
case presented splenomegaly for years, and hemorrhagic phenomena
before death. There was myeloid metaplasia of the spleen with de-
struction of the lymphoid follicles, myelosis of the liver, and myeloid
infiltration of the kidney and skin. The bone marrow appeared normal.

NATURE OF ALEUKEMIC MYELOSIS

It is a well known fact that in embryonic development hematopoietic
tissue normally occurs in extra-osseous locations, notably in the spleen
and liver. When the function of blood formation is acquired by the
bone marrow of the fetus there is a regression and disappearance of the
extra-osseous foci which reappear in later life only under pathologic
conditions. The return of hematopoietic activity to the spleen, liver,
and lymph nodes under conditions in which it is obviously compensa-
tory to blood loss, destruction, or a maturation deficiency, is sufficient
grounds for the assumption that constant potentiality exists in these
extra-osseous tissues to revert to hematopoiesis. As far as is known,
only one common functional and anatomic relationship exists between
bone marrow, liver, spleen, and lymph nodes: the reticulo-endothelial
system. Although controversial, it seems likely that it is the prolifera-
tion and differentiation of the reticulo-endothelial cells that produces
hematopoietic tissue in the extra-osseous localities under certain patho-
logic conditions.

It has not been fully established whether the extra-osseous myelosis
in leukemia is a manifestation of local origin or the result of coloniza-

tion (metastasis).[68,69] The myeloid infiltration of viscera, such as kidney and lung, which do not possess an intrinsic reticulo-endothelial system,* can be explained only by the assumption that such foci are the result of continuous proliferation of immature myeloid cells arriving in these viscera through the blood stream. However, such an interpretation for the myelosis of organs possessing a reticulo-endothelial system does not necessarily obtain and our observations refute such an *exclusive* interpretation.

In our cases the local origin of the myeloid cells in the spleen, liver, and lymph nodes appeared to be well established both by direct histologic features and indirectly by inference. Histologically, the development of megakaryocytes and myeloblasts from the reticulo-endothelial cells was observed through numerous transitional forms. Inferentially, the absence of immature myeloid cells from the blood seemed to preclude their appearance in spleen, liver, and lymph nodes by a process of leukemic colonization. This is particularly significant in reference to the megakaryocytes. Although such cells have been described in the blood,[70] they represent fixed cells not prone to be widely disseminated by the vascular system. Furthermore, the occurrence of an occasional megakaryocyte in the circulating blood would scarcely explain the diffuse megakaryocytic reaction of the extra-osseous myelosis exhibited in our cases.

It has been claimed that the failure to demonstrate immature leukocytes in the blood does not exclude a metastatic process in leukemia. An analogy is drawn with extensive carcinomatosis in which tumor cells cannot be demonstrated in the blood.[44] The analogy is not fully valid. Theoretically, each metastatic tumor in carcinomatosis may represent vascular dissemination of only one tumor cell which gives rise to a large secondary growth through continuous proliferation. The most extensive carcinomatosis represents vascular dissemination of only a relatively few tumor cells and their detection in a blood smear would be a fortuitous rarity. In myelogenous leukemia, the diffuse character of the leukemic infiltrations suggests that the majority of the cells are individually metastatic. These infiltrations do not represent, as in carcinomatosis, a solid compact tumor mass having origin from a single metastatic cell. Hence, the absence of immature myeloid cells in the blood stream of cases such as we have reported is indirect evidence supporting the theory of local origin of the myelosis. Furthermore, the metastatic concept does not adequately explain the invariably predominant distribution of the myelosis to liver, spleen, and lymph nodes.

* Distinction is made between the sinusoidal endothelium of the reticulo-endothelial system and the interstitial mesenchymal reticulum cells. The above comment is in reference to the former.

The occurrence of myeloid metaplasia in spleen and elsewhere in diseases unrelated to leukemia, in which the factor of colonization or metastasis is not an issue, offers strengthening evidence for local origin. The observations of many investigators support this concept.[17,28,50,66,71-76]

It appears likely that aleukemic myelosis is the expression of some obscure stimulus acting upon the reticulo-endothelial system, resulting in abnormal proliferation and differentiation of reticulo-endothelial cells into myeloid cells. It appears probable that the abnormal growth stimulus is the same as that operating in myelogenous leukemia, but quantitatively altered in this disorder, generally resulting in a myeloid proliferation of reduced intensity, of more prolonged course, and productive of a more diversified and more highly differentiated cellularity. Under this abnormal stimulus the reticulo-endothelial cells are capable of differentiating into either megakaryocytes or granulocytic cells, some of which may escape into the circulating blood. Their relative maturity serves to explain the absence of general leukemic infiltrations of viscera. Such cells do not inherit the same degree of growth potentiality as the more anaplastic cells which characterize the usual case of leukemia in which visceral infiltrations of organs not possessing an intrinsic reticulo-endothelial system can be explained only on the basis of colonization. Capability of reproduction does not seem to be possessed by myeloid cells at stages of development beyond the myeloblast. The capability of reticulo-endothelial cells under either normal or pathologic conditions to differentiate into megakaryocytes and myeloid cells has been described previously.[42,69,72,74,75]

The scope of such a concept obviously encompasses the myelosis of leukemia generally, in which the entire reticulo-endothelial system responds as a unit to the obscure leukemic stimulus. With such an interpretation, much of the myeloid reaction in organs possessing a reticulo-endothelial system, such as spleen and liver, may represent generation *in situ* and not a colonizing process. This would modify the interpretation that myelogenous leukemia is a disorder predominantly or even primarily of bone marrow. Such a concept is not new [1,10,44,50] but it has not received wide acceptance.

Incidence. The apparent rarity of genuinely aleukemic myelogenous leukemia (aleukemic myelosis) appears to be due, largely, to a misconception of the clinical, hematologic, and pathologic findings. When one incorporates with the leukemias the numerous cases of the type that we have reported and which are described under the many nonleukemic designations, the incidence is materially increased. A recent review [37] of the literature in reference to sclerosis of bone of the type associated

with aleukemic myelosis recorded 75 cases. A considerable number of cases of aleukemic myelosis without osteosclerosis appear in the literature. Consideration of these factors leads one to conclude that the disease is not rare. This is consistent with the experience of Baldridge and Fowler [7] who reported a permanently aleukemic state in approximately 5 per cent of their cases of diffuse myelosis (myelogenous leukemia). Incomplete data, individualistic nomenclature, the inclusion of cases of aleukemic myelosis in series with unrelated diseases, and the difficulty of formulating exact criteria to classify the numerous cases intermediary between aleukemic myelosis and chronic myelogenous leukemia render a complete and accurate compilation of recorded cases impossible, and this we have not attempted.

Diagnosis. Familiarity with the clinical features of aleukemic myelosis is one of the most important factors in the clinical diagnosis of the disease. Of foremost importance in the differential diagnosis are the diseases causing splenic enlargement. In many cases the presence in blood smears of granular leukocytes at various stages of immaturity, unexplainable by any infectious process, is presumptively diagnostic. It is important to stress the fact that an absence of immature leukocytes in the blood smear does not exclude aleukemic myelosis. Bone marrow studies may be diagnostic in those cases with myeloid hyperplasia; the great variability in the structure of the bone marrow, however, makes this procedure unreliable. In those cases with osteosclerosis, radiologic study of the bones will be strongly confirmatory. Diagnosis by splenic puncture is possible [1,2,28] but the results may be equivocal and the procedure is not without danger. In some cases the nature of the disease may be apparent only from autopsy study.

Treatment. In the majority of the reported cases the response to irradiation has been either indifferent or unfavorable. If radiotherapy is employed, the treatment should not be vigorous and the patient should be under careful observation. Splenectomy is contraindicated. Other therapeutic measures are merely symptomatic and supportive.

SUMMARY AND CONCLUSIONS

1. A study of three exemplary cases, with a review of the appropriate literature, has led to the interpretation of a syndrome characterized by splenomegaly and nonspecific alterations in the blood as a form of myelogenous leukemia. Many cases of this type are genuinely aleukemic.

2. Although this disorder is not particularly rare, its leukemic nature has not been generally recognized because of atypical clinical, hematologic, and pathologic features. Its identity has been obscured

by a diversified terminology. Aleukemic myelosis is an appropriate designation.

3. Osteosclerosis may occur in the course of myelogenous leukemia. Its occurrence favors the development of an aleukemic state of the blood.

4. The criteria alleged to differentiate the disorder from leukemia do not withstand critical analysis.

5. Cases of the type reported present strong evidence to support the belief that much of the myeloid reaction of spleen, liver, and lymph nodes in myelogenous leukemia is not an expression of colonization (metastasis) but of myeloid transmutation of the local reticulo-endothelial system of these organs.

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DESCRIPTION OF PLATES

PLATE 50

Fig. 1. Case 1. Spleen. The cut surface is fleshy and studded with small dark nodules.

Fig. 2. Case 1. Spleen. A myeloid nodule containing numerous giant cells occupies the upper half of the field; compressed parenchyma appears below. × 120.

Fig. 3. Case 1. Blood smear showing giant platelet. × 1250.

PLATE 50

├────── 10 cms. ──────┤
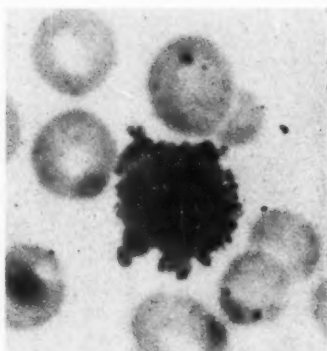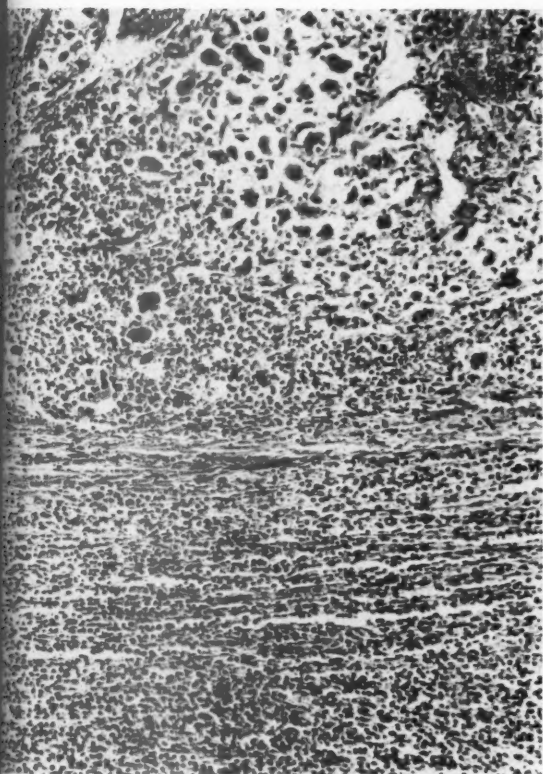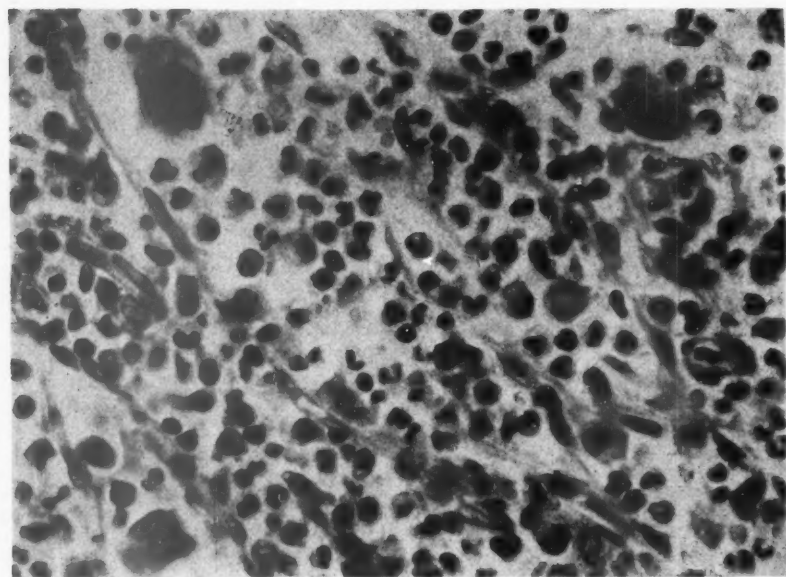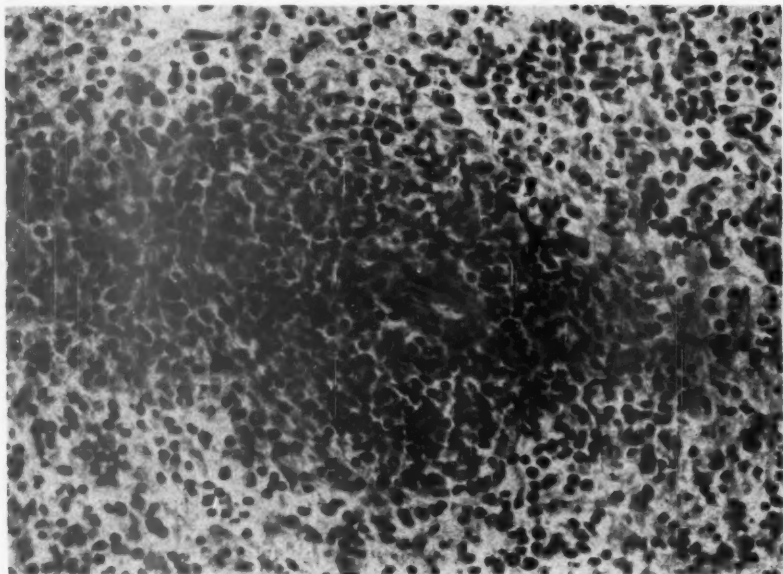
Heller, Lewisohn, and Palin

Aleukemic Myelosis

PLATE 51

FIG. 4. Case 2. Spleen. A lymphoid follicle is surrounded by myeloid tissue containing many giant cells of megakaryocytic type. × 300.

FIG. 5. Case 2. Spleen. Development of myeloblasts from reticulo-endothelial cells within the lumen of a sinus. Of note is the continuity of the myeloblasts with transitional forms of endothelium. × 650.

4
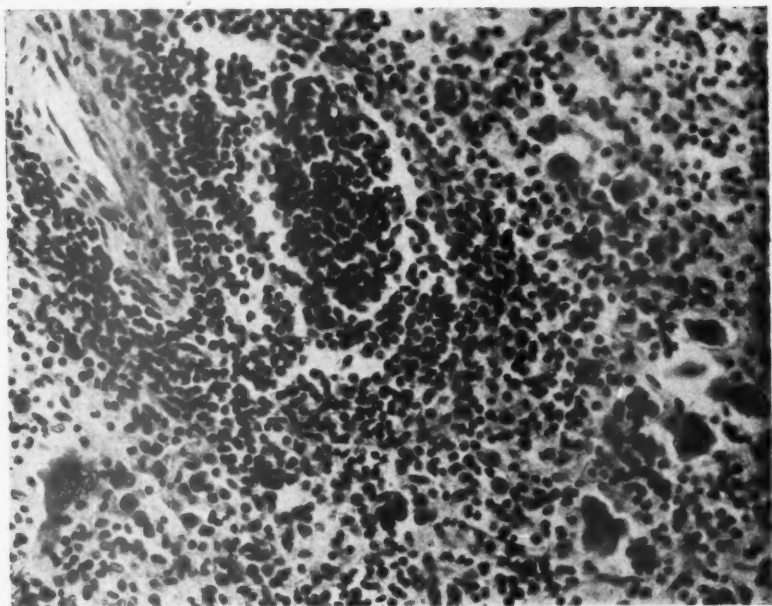
5
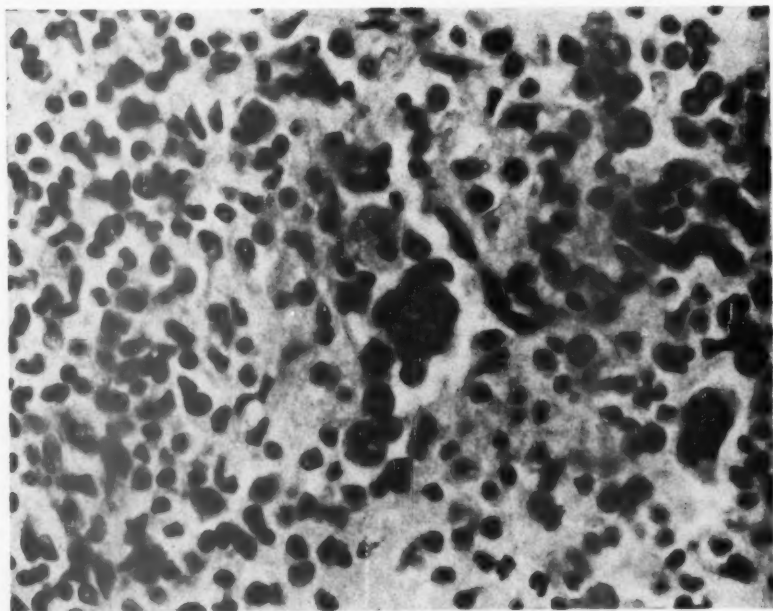
Heller, Lewisohn, and Palin

Aleukemic Myelosis

FIG. 6. Case 2. Spleen. Development of megakaryocytes from reticulo-endothelial cells. In the left upper area of the sinus there is an elongated tri-nucleated megakaryocyte. This cell represents a transitional form from the sinus endothelium. × 650.

FIG. 7. Case 2. Bone marrow, showing myeloid hyperplasia of pleomorphic type with numerous megakaryocytes. × 300.

6
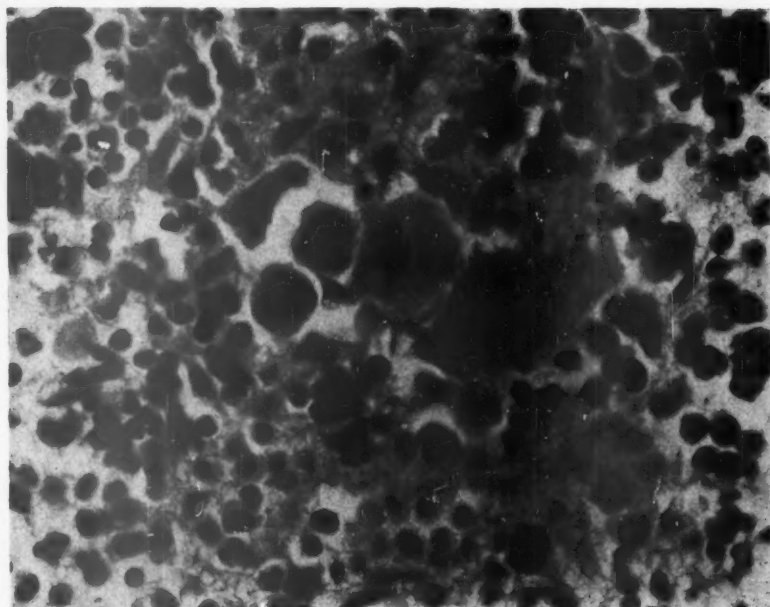
7
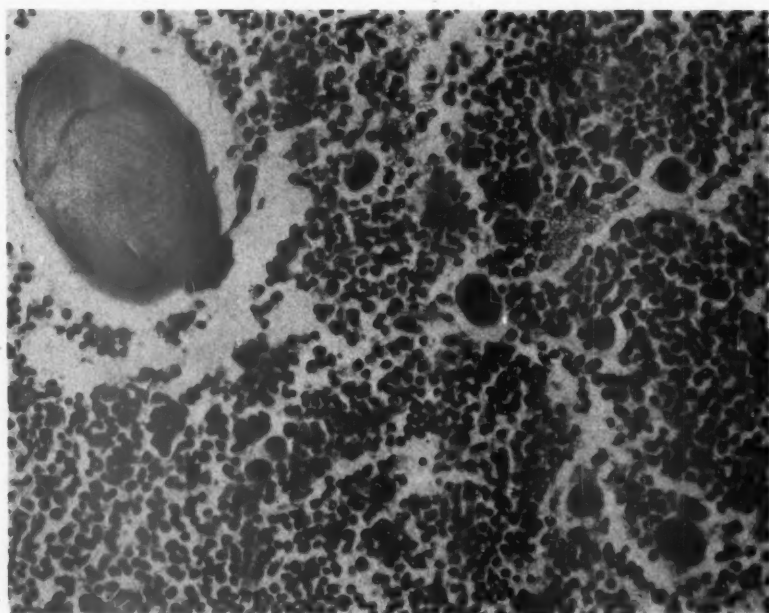
Heller, Lewisohn, and Palin   Aleukemic Myelosis

PLATE 53

FIG. 8. Case 2. Liver. Intrasinusoidal myelosis with numerous megakaryocytes. × 120.

FIG. 9. Case 2. Liver. Development of megakaryocytes from sinus endothelium. The multinucleated cell in the right half of the field represents an early stage of development. × 650.
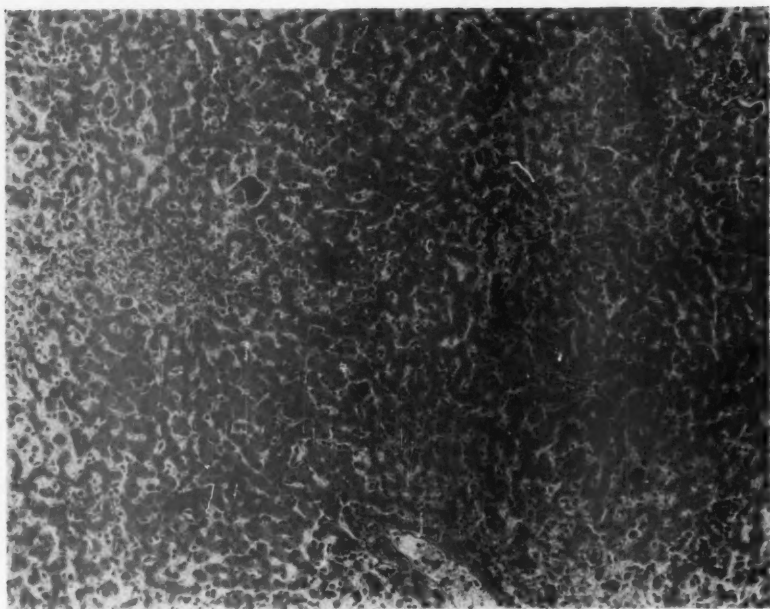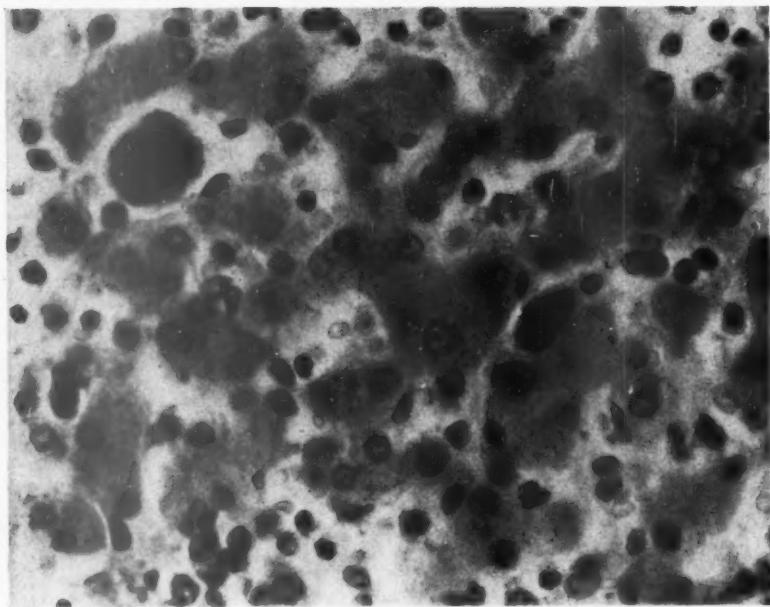
PLATE 53

Heller, Lewisohn, and Palin

Aleukemic Myelosis

PLATE 54

FIG. 10. Case 3. Spleen. Remnant of lymphoid follicle infiltrated by myeloid tissue. × 300.

FIG. 11. Case 3. Lymph node. Diffuse myelosis with three giant cells. × 650.

10

11

Heller

Plate 54

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Aleukemic Myelosis

FIG. 12. Case 3. Bone marrow. Diffuse myeloid hyperplasia. $\times$ 120.

FIG. 13. Case 3. Liver. In the left half of the field the portal stroma is infiltrated with myeloid cells. There is a similar involvement of the sinusoids. $\times$ 300.

12

13
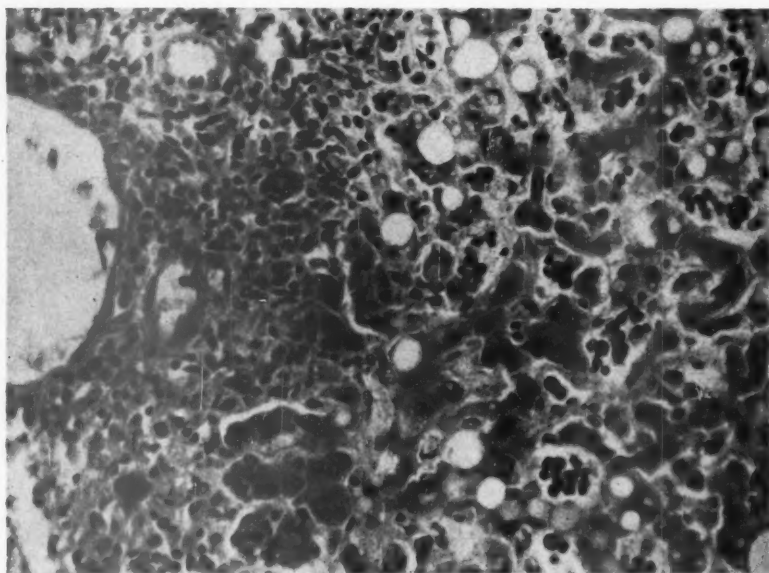
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Aleukemic Myelosis

LESIONS FOLLOWING THE USE OF ERTRON IN RHEUMATOID ARTHRITIS *

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The literature is replete with reports of the administration of various preparations of vitamin D, principally in the therapy of rickets and rheumatoid arthritis. Toxic symptoms in the form of anorexia, nausea, headache, polydypsia, and polyuria are known to occur with varying doses. That anatomic lesions must occur is manifest by the urinary changes and by tests showing impaired renal function and chemical alterations in the blood.[1-5] Only five patients whose deaths have been ascribed to large doses of vitamin D have been autopsied and all were infants.[6-9] Because lesions observed at necropsy following the prolonged use of Ertron † have not been described previously, the following case report is of interest.

REPORT OF CASE

E. P., a white female artist, 63 years old, was admitted to Goldwater Memorial Hospital for the first time in December, 1942. She stated that she had had pains and progressive deformity of the joints of the extremities for 18 years. Until 2½ years before admission she had received no medical treatment. At that time she was given approximately 100 intramuscular injections of gold extending over a period of 1 year. Her condition improved, but had relapsed after 4 months. Otherwise her past history included nothing relevant to her present condition. Physical examination revealed marked deformity and limitation of motion of the joints of the extremities. There was scoliosis of the lower spine with convexity to the left. The heart was not enlarged and the rhythm was regular. The blood pressure was 168/98 mm. Hg.

The patient remained in the hospital with a normal or slightly subnormal temperature for approximately 3 months, during which time she received x-ray therapy to the involved joints in unknown amount. She was discharged as slightly improved.

Her second and final admission occurred in August, 1945. Approximately 18 months prior to readmission she had begun to take three or four capsules (150,000 to 200,000 international units) of Ertron daily and had continued this dosage for 1 year without medical supervision. Six months before her second admission a lesion described as an "infection" developed on the right foot and discharged thick yellowish pus. Following this, numerous abscesses appeared over the dorsa of both feet, the left knee, and the dorsum of the right hand. Generalized pruritus was present but no rash was noted. The patient developed a chronic cough productive of brown but not bloody sputum. The weight loss was severe but indefinite in amount. No information was available concerning the patient's diet.

Physical examination on admission showed an emaciated, elderly female with

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marked deformities of the joints. Several small, discrete, nontender lymph nodes were palpable in the axillae, and in the inguinal and femoral regions. There was a draining sinus posterior to the medial malleolus of the right foot and multiple, tender, cystic swellings on the dorsum of the right hand, the left knee, and the left foot. The heart was regular and no murmurs were heard. The blood pressure on admission was 125/85 mm. Hg.

Course. During the patient's stay in the hospital, one of the abscesses was incised and a portion of the wall was examined microscopically. The report was "chronic nonspecific inflammatory reaction with calcification." Culture of the material from the draining lesions yielded *Staphylococcus aureus* on two occasions. This was thought to be a contaminant, but following penicillin therapy the cultures became sterile. The temperature on three occasions rose to 100°F. but averaged

TABLE I

Laboratory Data

	1943	1945
Hemoglobin	12.8 gm.	6 gm.
Red blood cells	4,600,000	2,500,000
White blood cells	7,500	7,800
Erythrocyte sedimentation rates	72 mm. per hr., Westergren	
Fasting blood sugar	107 mg. %	100 mg. %
Blood urea nitrogen	18 mg. %	58 to 107 mg. %
Blood nonprotein nitrogen		172 mg. %
Total protein		6.6 gm. %
Serum albumin		4.9 gm. %
Serum globulin		1.6 gm. %
Calcium		13 to 14.7 mg. %
Phosphorus		6 mg. %
Alkaline phosphatase		9.6 Bodansky units
CO_2-combining power		68 vol. % falling to 35 vol. %
Urine	Alkaline; albumin, trace; glucose, negative; many white blood cells	10 days before death: alkaline; albumin, +; glucose, +; few epithelial cells; few white blood cells (later examinations not recorded)

about 99.4°F. The patient's urea nitrogen rose progressively from 58 on admission to 107. Blood pressure never rose above 125/85 mm. Hg. She became moribund and expired about 1 month after admission.

Summary of Roentgenologic Findings. The roentgenologic examinations of the chest in 1943 and 1945 revealed no calcific deposits in the pulmonary parenchyma. In 1943, the wrists, hands, and knees showed the characteristic changes of rheumatoid arthritis (Figs. 1, 4, and 5). These changes were extensive, with bone decalcification, destructive changes, contractural deformities of the hands, and ankylosis of the wrists. The left knee showed osseous destruction while the right showed cartilaginous destruction only. The vessels about the joints were not calcified and there were no calcific deposits in the soft tissues.

In 1945, the wrists, hands, and knees showed progressive changes due to arthritis. Despite these changes, the bones were denser and presented a more nearly normal appearance than in 1943. In fact, the entire skeleton was richer in calcium content. The vessels about the joints were calcified, notably the pelvic, femoral, popliteal, and tibial arteries. The deposition of calcium in the soft tissues presented striking appearances. The synovial membrane of the left knee was completely outlined, showing its extent, distribution, and lobulations. Calcium was also deposited within

the joint (Figs. 6 and 7). Considerable calcium was deposited in the soft tissues in
and about the right wrist, thenar eminence, fingers of the right hand, and in the
interosseous membrane of the forearm. Soft tissue swellings about the wrist and
on the dorsal aspect of the hand contained calcium (Figs. 2 and 3). There was less
calcium in the left hand, the deposit being limited to the proximal interphalangeal
articulation of the ring finger; there was destruction and subluxation of the under-
lying joint.

Similar changes were observed in the elbows. The destructive changes were
pronounced and there was calcium deposited in and about the joints, especially on
the left side. Soft tissue lobulations about the joints were outlined by calcium
salts. The ankles were free of destructive osseous changes but the metatarsophalan-
geal articulations were not. Large amounts of calcium were deposited in the soft
tissues in and about the ankles and in the joints of the feet as well as in the
Achilles tendon. A notable collection was present in and about the metatarsophalan-
geal articulation of the right big toe. A rather unusual collection was observed in
the soft tissues of the left leg extending 13 cm. above the ankle, medial and
posterior to the fibula (Figs. 8 and 9).

Comparative study of roentgenographs of the lumbosacral spine in 1943 and 1945
showed no marked changes. There were no calcific deposits in or about the
shoulders.

Necropsy

Necropsy was performed 13 hours after death.

The deformities of the joints and other parts of the body were those
noted on physical examination. The mouth was edentulous. Discrete
but small lymph nodes were present in each axilla. Thick, chalky
material was seen at the sternoclavicular joint and at several of the
costochondral junctions. Fibrous adhesions were present over both
apices and there was a rim of dense parenchyma beneath the apical
pleura on both sides. This extended to a lesser degree around the ad-
jacent periphery of the lungs. A few, firm, light pink areas bulged
above the surface in all except the right middle lobe. The lungs were
rust-colored and exuded large quantities of frothy material. The peri-
bronchial lymph nodes were anthracotic.

The heart with the densely adherent pericardium weighed 360 gm.
The surfaces were shaggy. The endocardium of the left auricle was
not thickened. The mitral valve was not deformed and the chordae
tendineae were delicate. The remaining valves were normal. There
was a moderate amount of diffuse sclerosis of the coronary arteries but
the lumina were patent. The ostia of the renal arteries were narrowed
by sclerotic plaques. The pancreas was irregular, the normal pa-
renchyma being replaced in the head and tail by ill defined, firm,
yellow masses which on section exuded from their centers small
amounts of thick, putty-like material. No dilatation of the ducts was
noted and the remaining parenchyma was apparently normal. The kid-
neys were small, weighing 60 gm. each. The surfaces were smooth
but there were numerous punctate red areas. The cortices were re-
duced and the pelves, ureters, and urinary bladder were normal.

Cultures of the fluctuant areas of the right hand, left foot, pancreas, and fluid from the knee joint were sterile.

On microscopic examination of the left auricle, the endocardium was found to be slightly thickened by edema and connective tissue. The subendocardial portion of the auricular myocardium was replaced by a series of poorly circumscribed granulomatous lesions (Fig. 10). These were made up of partially calcified, amorphous, necrotic material surrounded by hyaline connective tissue, radially arranged fibrocytes, bizarre-shaped pyknotic nuclei, and a few multinucleated giant cells. In the cytoplasm of these were particles of calcium. The myocardial fibers at the periphery of the nodules were fragmented but there was little cellular reaction about them (Fig. 11). That which was present was composed of a few lymphocytes and Anitschkow myocytes. The lesions were poorly vascularized, but in the myocardium surrounding them were several capillaries. The mitral valve showed a few vessels with intimal thickening, but was otherwise not unusual. The mitral ring contained calcium. The endocardium of the left ventricle was normal. The myocardium showed a few areas of perivascular scarring which replaced small numbers of adjacent myocardial fibers. Most of the epicardial fat of the left ventricle was replaced by a thick fibrous band of dense but well vascularized connective tissue. The surface was covered by fibrinoid exudate which was partly organized. A few polymorphonuclear leukocytes were found in the fibrous tissue.

Numerous sections through various parts of the heart showed nothing unusual. There was moderate perivascular scarring and a small amount of intimal proliferation in the small branches of the coronary arteries, but no Aschoff nodules were seen.

Sections from the peripheral portions of both lungs showed replacement of the normal architecture by fibrous tissue (Fig. 12). In some areas the alveolar septa persisted but were greatly thickened and the alveoli were reduced in size. Within the fibrous tissue were multinucleated giant cells and masses of calcium. Aggregations of necrotic polymorphonuclear leukocytes and fibrin persisted in the midst of the fibrous tissue. The bronchial epithelium in a few places contained calcium. Beneath the epithelium were spicules of calcium which had eroded the epithelium and projected into the lumen. The lumina also contained purulent exudate and coagulum. The alveolar lining, when present, consisted of a single layer of flat cells outlining the irregular dilated spaces. Some of the septa were completely calcified (Fig. 13). The vessel walls were thickened by intimal proliferation of connective tissue and calcium was deposited in a rim about the adventitia. Other

sections from the right apex showed masses of necrotic purulent exudate in hyalinized scar tissue. Fresh exudate with colonies of gram-positive cocci was noted in one area.

The thyroid contained numerous nodules composed of acini which varied in size and were surrounded by connective tissue. The small amount of calcium deposited in the scar tissue was not unusual.

One parathyroid appeared normal except for a minute cyst filled with colloid. A nodule removed as parathyroid was composed of spicules of calcium, foreign body giant cells containing particles of calcium, and fibrocytes (Fig. 14).

In the pancreas there was extensive necrosis, both of the interstitial fat and parenchyma. In abscess cavities were masses of fibrin and polymorphonuclear leukocytes. All stages of healing were seen in various sections. In large areas the parenchyma had been replaced by dense scar tissue. In these areas the ducts were dilated and filled with amorphous pink coagulum but the epithelium was normal (Fig. 16). Giemsa's and Brown's * stains failed to reveal bacteria in the areas of acute exudation. There were no calcium deposits.

Some renal glomeruli were small and shrunken, and a few were hyalinized with the capsules of Bowman thickened. The afferent arterioles and basement membranes were also slightly thickened by hyalinized connective tissue in a few areas. There was reduction of both cortex and medulla due to atrophy and disappearance of tubules, but the renal papillae were not blunted. Scattered throughout the parenchyma, but principally in the medulla, were minute foci of necrotic polymorphonuclear leukocytes, lymphocytes, and plasma cells which seemed to represent necrotic tubules filled with polymorphonuclear leukocytes, the walls of which had ruptured. In many places these small abscesses were healing. All tubules were disarranged; many were distended with various types of casts, others showed necrotic walls, and still others, hyperplasia of the epithelium. Many tubules were atrophic and filled with hyalinized and granular coagulum. A few showed calcified casts (Fig. 15). The interstitial tissue was edematous but remarkably free of infiltration except about the granulomatous lesions. The walls and pelvic epithelium were not unusual. The renal arteries showed moderate sclerosis, but calcium deposits were lacking. With von Kossa's stain large amounts of calcium which were not apparent in the hematoxylin and eosin preparations were demon-

* Brown, J. H., and Brenn, L. A method for the differential staining of gram-positive and gram-negative bacteria in tissue sections. *Bull. Johns Hopkins Hosp.*, 1931, 48, 69–73.

strated in the granular casts and in the epithelium and basement membranes of the tubules. The calcium occurred in both the convoluted and collecting tubules.

The lymph nodes revealed focal areas of necrosis similar to those found in the pancreas and kidneys. The sinusoids were filled with polymorphonuclear leukocytes.

Sections of the chalky deposits about the ribs and clavicles showed masses of amorphous material containing calcium which spread into the surrounding muscle. Many of the individual muscle fibers showed partial calcificatior. No osteoporosis or evidence of acute inflammation was noted.

Sections of the aorta and its major branches showed sclerotic changes of no more marked degree than might be expected in any patient of the same age.

With Brown's and Gram's stains no bacteria were found in the lymph nodes, heart, and kidneys.

Anatomical diagnoses included: Chronic rheumatoid arthritis; calcinosis involving the periarticular tissues of the extremities, the sternoclavicular joints, the costosternal articulations, the subcutaneous tissue, the myocardium of the left auricle, the lungs, and the kidneys; lobular pneumonia; acute and chronic pancreatitis with abscess formation.

COMMENT

The cardiac lesions observed in the left auricle are not essentially different from those described by Baggenstoss and Rosenberg[10] as occurring in rheumatoid arthritis, except that the calcification in this instance is much greater and the giant cells contain particles of calcium. Involvement of the myocardium and not of the adjacent auricular endocardium is unusual for a lesion of rheumatic origin, yet the situation in the left auricle suggests this causal factor. It is probable that this is a lesion similar to those found in the other organs. It does not resemble the degeneration and vacuolization of the myocardial fibers mentioned by Malmberg[6] as occurring following cod-liver oil therapy. The pericardial lesions had nothing to distinguish them from an organizing fibrinous pericarditis of long duration. No mention is made of the pericardium in any other cases. In this instance the pericarditis may be a manifestation of long-standing uremia, although its severity and wide distribution make this unlikely.

Despite evidence in the roentgenograms of increase in calcium in the peripheral vessels of the lower extremities, sections of the aorta and of the renal, iliac, and hypogastric arteries showed only arteriosclerosis of mild degree.

The lesions in the lung were apparently unique. It may be argued that the necrotic foci surrounded by polymorphonuclear leukocytes in the midst of the fibrous tissue are an indication of organizing pneumonia which in turn has caused the fibrous tissue proliferation. Be that as it may, we have never observed this bizarre type of calcification in other pneumonias. The location of the calcium suggests that its deposition was influenced by the rapid change in pH which occurs in the alveolar spaces.

The presence of calcium in the skin and in the periarticular tissues in conjunction with a hypercalcemia coincides with the observations of many authors.[2,8,5]

The density of all the bones was increased following the use of Ertron. This suggests that the excessive calcium was being derived from sources other than bone.

Calcium deposits have been noted grossly in the kidneys of both children and experimental animals which have received large amounts of vitamin D. Localization in and about the tubule has been recorded by many observers.[6-9,11] Calcium deposition in the kidney was not as conspicuous in the case reported here. It was demonstrated in the lumina as well as the walls of the tubules. The glomerular changes were slight. The pelves and ureters showed no evidence of previous or recent damage. The localization of the acute lesions to the tubules is interesting to note, for if this were a disseminated hematogenous lesion of a septic nature, one would expect the glomeruli to be involved. We are aware that the kidneys may have been damaged by the therapeutic use of gold, but the fact that the urea nitrogen of the blood was normal 18 months after the cessation of such therapy suggests that the damage was not severe. The lesions of the tubules were of sufficient severity to account for the mounting urea nitrogen of the blood as observed clinically.

Since impaired renal function and nitrogen retention are known to occur in connection with the toxic action of vitamin D, both in lower animals and man, and since these signs developed in this patient following the prolonged use of this substance, it seems fair to assume that vitamin D played some rôle in the clinical picture of renal insufficiency.

The pancreatic lesions were similar to those seen in the kidney, except that calcification was lacking. The persistent finding of 1 plus glucose in urinalyses may have been due to a direct effect upon the islets of Langerhans, although in the sections examined these seemed normal and numerous. No mention is made of pancreatic lesions in necropsy reports of children, or in animal experiments.[12]

The nodule removed as parathyroid was difficult to interpret. It

showed only fibrous tissue, calcium, and foreign body giant cells re-
sembling those seen in the lungs and skin. The thyroid gland showed
no such reaction, so that contiguity with this structure seemed unlikely.
The other parathyroid was normal.

It is possible that this patient had a low-grade sepsis with multiple
granulomatous lesions occurring in various parts of the body, the
causal agent of which was obscure. However, hypercalcemia, and depo-
sition of calcium in the periarticular tissues, alveolar septa, left auricle
and kidney tubules can scarcely be attributed to sepsis. We are
tempted to include the lesions of the pancreas and lymph node, and
the uncalcified pulmonary lesions as additional manifestations of the
same disturbance.

Summary and Conclusions

Unsupervised use of Ertron in a patient suffering from rheumatoid
arthritis led to hypercalcemia, and calcium deposition in the periarticu-
lar and subcutaneous tissues, lungs, heart, and kidneys.

There were chronic and acute granulomatous lesions in the lungs, the
pancreas, the kidneys, and the lymph nodes, the nature of which was
obscure. It is suggested that these lesions also are related to the use
of Ertron.

Extensive damage to the renal tubules formed an anatomic basis for
clinical renal insufficiency.

Since this paper was submitted for publication two reports have appeared de-
scribing similar lesions observed at necropsy in adults, following extensive use of
vitamin D preparations. (Bauer, J. M., and Freyberg, R. H. Vitamin D intoxica-
tion with metastatic calcification. *J. A. M. A.*, 1946, **130**, 1208–1215. Mulligan,
R. M. Metastatic calcification associated with hypervitaminosis D and haliphagia.
Am. J. Path., 1946, **22**, 1293–1305.) The opinions expressed by these authors
corroborate the statement that various acute and chronic lesions as well as calci-
fication are related to excessive vitamin D ingestion.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 56

FIG. 1. Right wrist, 1943. Advanced rheumatoid arthritic changes. Fusion of the residuals of the carpal bones with ankylosis. Contraction deformities of fingers; destructive changes involving the metacarpophalangeal articulations of the right hand. Decalcification of bones.

FIGS. 2 and 3. Right wrist and hand, 1945. Extensive progression of the lesion. Of note is the irregular deposition of calcium in and about the bones of the right wrist and hand, in the periarticular soft tissues, the thenar eminence, the soft tissues of the fingers, and in the interosseous space. Density of the bones is greater than in Figure 1.

1

2

PLATE 57

FIGS. 4 and 5. Left knee, 1943. Destruction of articulating cartilages and subchondral bone with bone sclerosis on contiguous surfaces of femoral and tibial condyles. Effusion in the joint and suprapatellar bursa. Moderate decalcification. No calcific deposits in the soft tissues. The vessels are not calcified.

FIGS. 6 and 7. Left knee, 1945. Of note are the progressive arthritic changes and increased bone density. Lateral subluxation and dense lobulated calcific deposit in the soft tissues corresponding to the synovial membrane of the knee joint. Calcific deposits in the soft tissues and in the walls of the femoral, popliteal, and tibial arteries. Increased calcification in the upper end of the tibia.

Figs. 8 and 9. Left ankle and foot, 1945. Calcium deposited in the soft tissues in the lower third of the leg, about the tarsal bones and ankle. Large lobulated collections of calcium in the soft tissues posterior and medial to the shaft of the fibula.

Fig. 10. Left auricle showing extensive calcification of subendocardial myocardium. Von Kossa's stain. $\times$ 40.

Beva

PLATE 58

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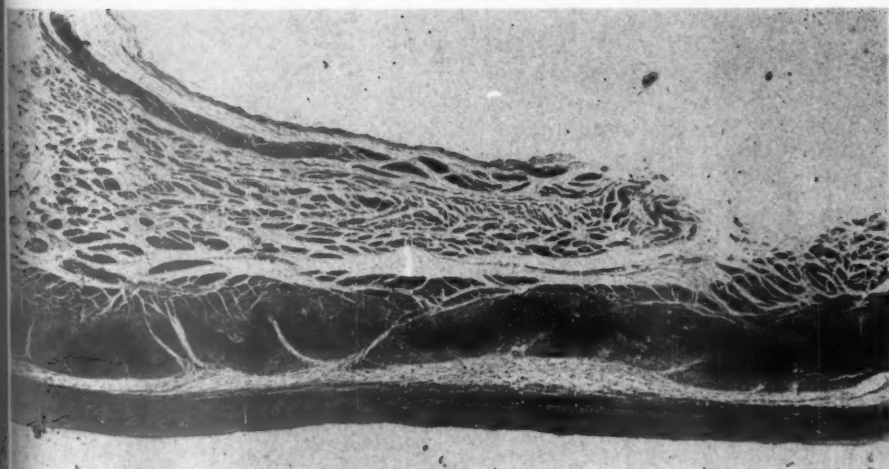
Bevans and Taylor

Effects of Ertron

FIG. 11. Higher magnification of granulomatous lesions replacing the myocardium of the auricle. Hematoxylin and eosin stain. × 165.

FIG. 12. Section of lung showing extensive fibrosis. Hematoxylin and eosin stain. × 35.

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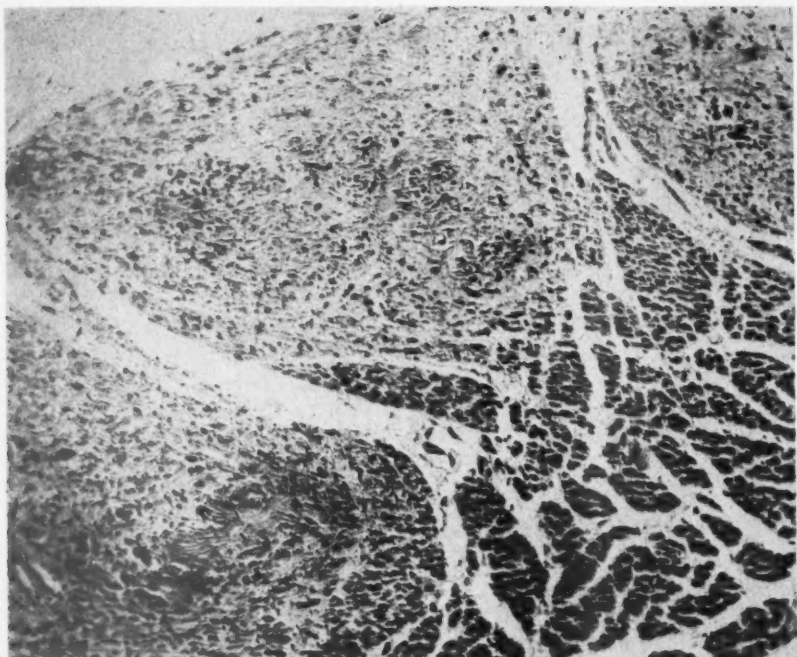
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PLATE 60

FIG. 13. Higher magnification of lung. Two spicules of calcium in the alveolar septum appear to the left of the center. A foreign body giant cell is present at the lower right. Hematoxylin and eosin stain. × 515.

FIG. 14. Tissue removed as parathyroid. Granulomatous lesion typical of that seen also in the heart and lungs. Of note are the foreign body giant cells with particles of calcium within the cytoplasm and free calcium throughout the lesion. Hematoxylin and eosin stain. × 615.

AME

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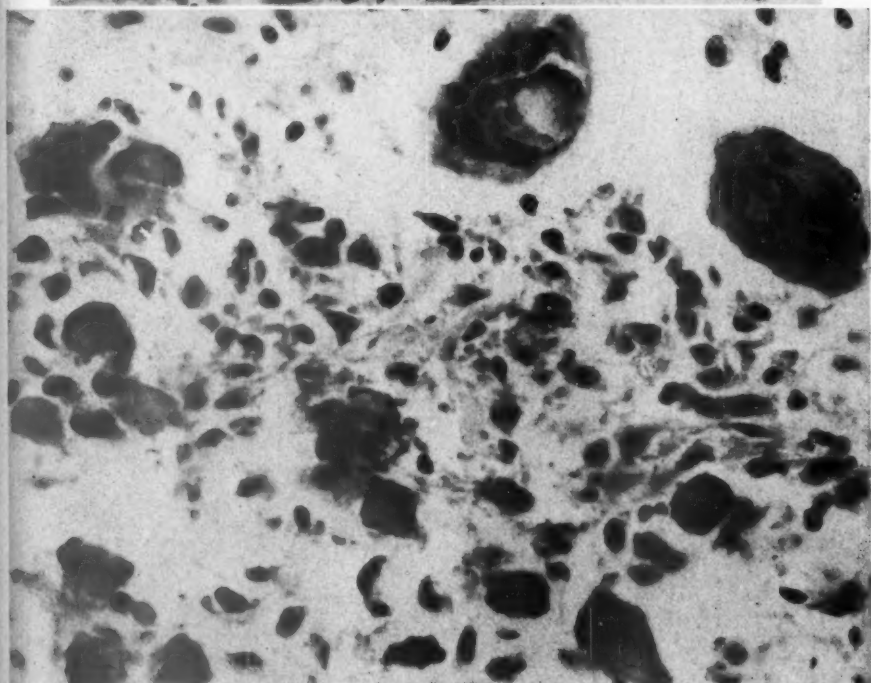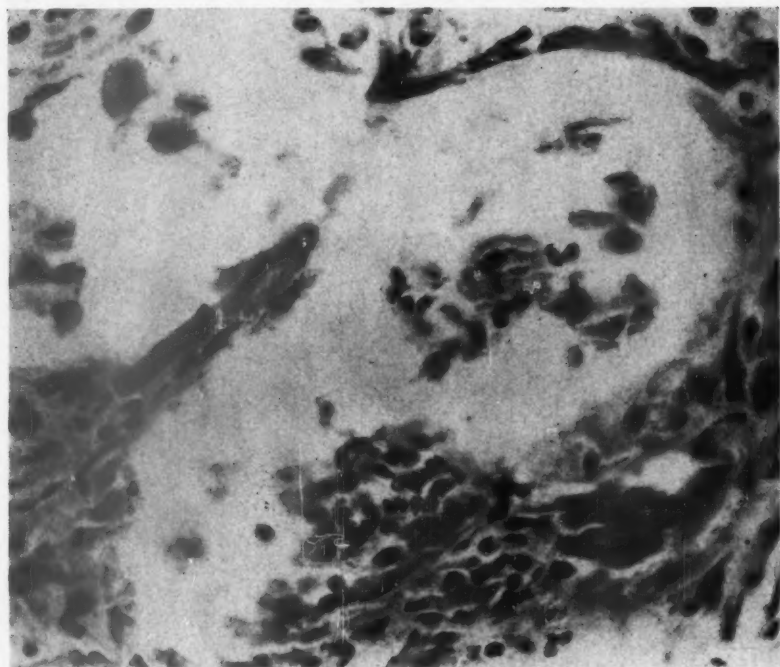
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Effects of Ertron

PLATE 61

FIG. 15. Kidney showing atrophic tubules and calcified cast at the right. Hematoxylin and eosin stain. $\times$ 125.

FIG. 16. Pancreas showing necrosis and fibrosis. Hematoxylin and eosin stain. $\times$ 40.
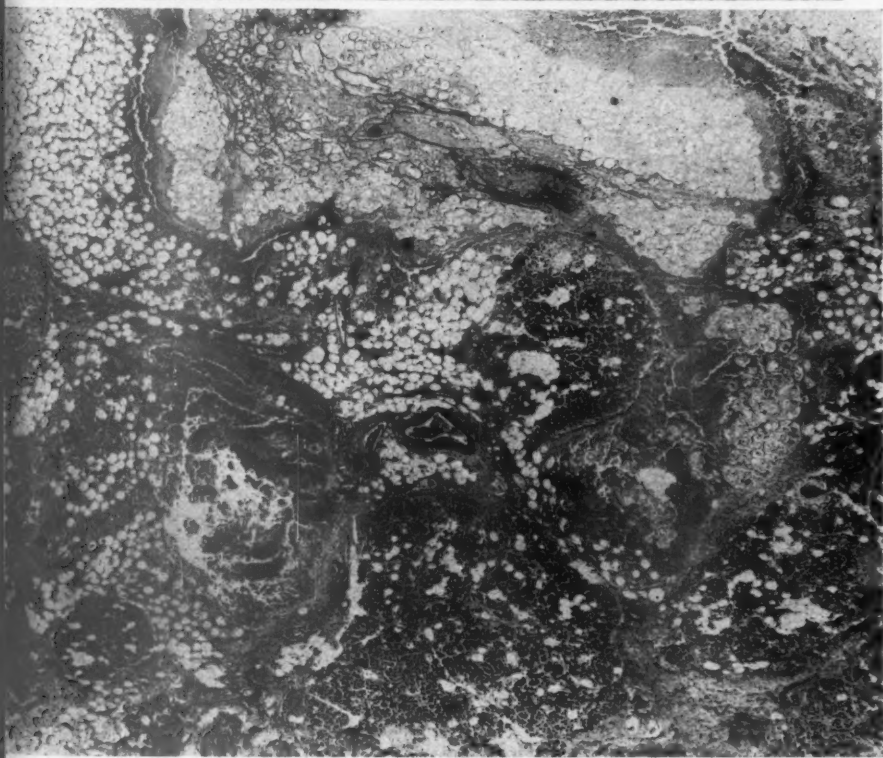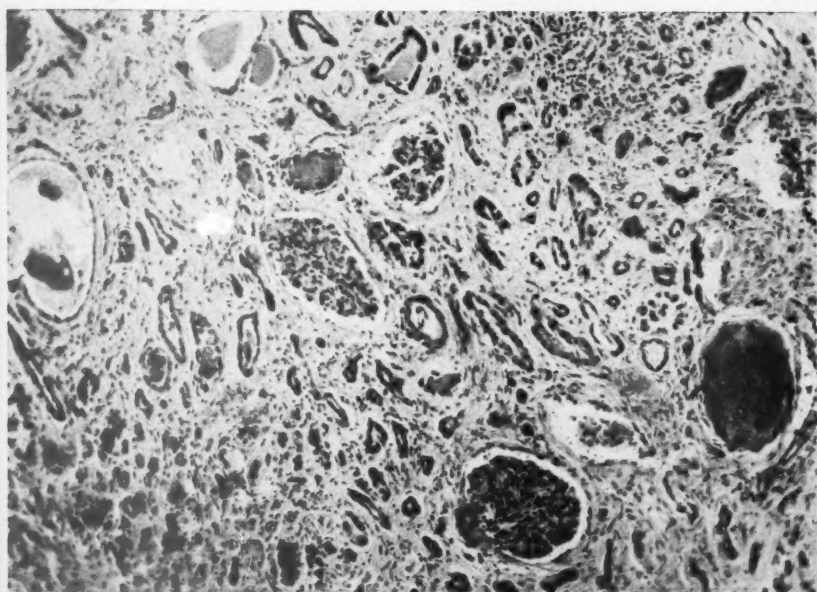
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Effects of Ertron

RADIO-AUTOGRAPHIC STUDIES OF THE DISTRIBUTION OF LEWISITE AND MUSTARD GAS IN SKIN AND EYE TISSUES *

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Radio-autography is a technic which utilizes the photographic property of radio-activity and is useful in studying the histologic distribution of an element or compound in the tissues of living organisms. Following the administration of a radio-active element or compound to an organism, samples of tissues are removed, and histologic sections are prepared. The sections of tissue, mounted on microscopic slides, are placed in contact with x-ray film. After a suitable period of exposure the film is removed, developed, and the sections are stained. The regions of darkening on the film represent areas where accumulation of the radio-active material has occurred in the tissue section. A correlation of the microscopic anatomy of the tissue and the distribution of the accumulated radio-active element or compound may be established.

The basic principles involved are as follows: (1) A total of from 2 to 10 million beta particles from the section must strike each square centimeter of the film to produce an adequate blackening. (2) The radio-active element or compound must be firmly fixed in the tissue so that the various conditions to which the tissue is subjected during the preparation of the sections will not leach it out. (3) The sections should be less than 10 μ in thickness to obtain maximum resolution. Satisfactory results are obtained with sections ranging in thickness from 5 to 8 μ; sections which are thinner do not give significantly superior resolution. The resolution obtainable varies to a considerable degree but under the very best conditions is 25 μ, which precludes the possibility of the study of the internal structure of individual cells. (4) The half-life of the radio-active agent used must be sufficiently long to permit the preparation of the sections, and there must remain an adequate radio-activity to produce a satisfactory radio-autograph.

The distribution in skin and eye tissues of two war gases, mustard and lewisite, has been studied using this technic. These substances were labeled with radio-active sulfur and radio-active arsenic, respectively.

METHODS

Skin and eye tissues were exposed to the two gases. The skin was thoroughly washed with petroleum ether to remove the residual applied material. The tissues were removed from the experimental animals after varying intervals and fixed in formalin. Skin was embedded in paraffin. Eye sections were prepared both by the paraffin technic and by freezing, the better sections being obtained by the latter method. Paraffin sections were cut 10 μ in thickness, while the frozen sections were approximately 15 μ. The sections were mounted on microscopic slides, and the paraffin was removed by xylol. The slides were then dipped in a dilute solution of celloidin and set on edge to dry. This procedure served to remove the paraffin from the sections since it would otherwise smear the emulsion, and to cover the slides with a thin, protective layer. Some experiments were done using unfixed, frozen tissues. Such tissues were frozen with dry ice immediately after excision and then cut on a freezing microtome.

Each slide was covered with a piece of no-screen x-ray film (Agfa), then carefully wrapped in black paper to exclude light, and finally placed under a lead weight in order to hold the film in close contact with the sections. After a suitable exposure (in these experiments, the times varied from 1 to 3 weeks for optimum blackening), the films were developed, the sections washed in ether-alcohol to remove the celloidin, and stained with hematoxylin and eosin. Each stained slide and its corresponding radio-autograph was examined microscopically; the regions of darkening on the radio-autograph were correlated with the histologic structures in the corresponding area on the section. The areas of darkening on the film correspond to the regions in the sections where the lewisite or mustard gas was accumulated.

It must be emphasized that radio-autographs indicate only the presence of the radio-element; this is probably also an index of the distribution of the compound, but the possibility must be considered that the radio-element could become separated from the original molecule by interaction with animal tissue fluids.

RESULTS

Studies with Mustard Gas on Human Skin

Two experiments were run with mustard gas labeled with radioactive sulfur, S^{35}, containing 5 microcuries of S^{35} per mg. of mustard and applied on human skin. The first exposure was for 10 minutes to 475 μg., and the second was for 15 minutes to 475 μg. of mustard; in each case, the area exposed was 0.43 square cm., and biopsy specimens of these areas were taken 24 hours after exposure. Essentially similar

results were obtained in both experiments. Radio-actively tagged mustard was fixed in the epidermis and in the corium (Fig. 1). The epidermal concentration was slightly higher than that in the corium. Hair follicles were seen rarely and it was difficult to determine whether or not they fixed mustard. In the dermis, the blackening of the autographs was so great as to make it difficult to determine the specific concentration by blood vessels. There does not appear to be any correlation between the radio-activity present and cell injury due to mustard since a large amount of fixed sulfur radio-activity was present despite the fact that few cells were injured. This effect may be due to the fact that morphologic evidence of injury requires longer than 24 hours for development after exposure to the gas.

Studies with Lewisite on Human Skin

Two experiments on human skin were run with lewisite labeled with radio-arsenic, As^{74}, and containing about 10 microcuries of As^{74} per mg. of lewisite; the first exposure was for 10 minutes to 475 μg. of lewisite and the second for 15 minutes to 475 μg. The areas exposed were 0.43 square cm., and biopsy specimens of the exposed areas were taken 24 hours after exposure. Results from both experiments were similar. The radio-autographs showed that the lewisite was concentrated primarily in epidermis with very little in the dermis (Fig. 2). Unlike mustard, from which no visible injury occurred, the radio-activity in the epidermis was confined almost exclusively to dead cells. In contrast to the mustard experiments, there was a massive necrosis of most of the epidermal layer and the corium. This is probably to be explained by the fact that the effect of lewisite is more rapid on the skin than mustard, and the injury is detectable within 24 hours. The small amount of lewisite present in the corium was found to occur in regions of perivascular exudate (Figs. 2 and 3), in some, but not all, of the hair follicles (Fig. 2), and in some blood vessels (Figs. 2 and 3). The hair follicles accumulated the lewisite to about the same degree as epidermis. In one case in which involvement of the hair follicles occurred, activity was present in an associated sebaceous gland (Fig. 2).

Studies with Mustard on Pig Skin

In the first studies with mustard applied on pig skin, the exposure was for 6 hours to 2 mg. of the material, and the exposed areas were excised 24 hours after application. Results showed that mustard concentration was greatest in the epidermis, a slightly smaller amount in the corium, and very little in the hypodermis. The small amount of mustard in the hypodermis was found principally in the bands of

fibrous tissue surrounding the fatty tissue and in the deep blood vessels. A considerable amount of mustard was noted in the hair follicles and adjoining sebaceous glands (Figs. 4 and 5). The radio-autograph in Figure 4 indicates the variety of deep structures that have accumulated the material. A relatively large amount of mustard appears in the fibrous structure approximately midway between the epidermis and muscle which is apparently a fascial plane. Below this layer of fascia and a short distance above the muscle tissue, two blood vessels have accumulated a considerable amount of mustard. A very large proportion of the total amount retained was present in the epidermis. The section in Figure 5 represents a higher magnification of the region which has been delineated in Figure 4. The deposition in sebaceous glands, subcutaneous fibrous tissue, and blood vessels can be seen in somewhat better detail here.

A 15 minute exposure to 475 μg. of mustard gas, with immediate excision of the pig skin, showed much less penetration of the corium as compared with the 6 hour exposure to 2 mg. The mustard penetrated downward as far as the papillary layer of the dermis, and superficially located hair follicles accumulated mustard (Fig. 6). The 15 minute exposure with excision 24 hours later showed penetration into the dermis with accumulation in hair follicles well below the epidermis (Fig. 7).

Studies with Lewisite on Pig Skin

Two specimens of formalin-fixed pig skin contaminated with lewisite were studied. Sample 1 was exposed to 1.269 mg. of lewisite for 15 minutes, 24 hours prior to excision. Sample 2 was exposed to 1.534 mg. of lewisite for 1 hour, 24 hours prior to excision. It is apparent from viewing the photomicrographs of the skin sections and their corresponding radio-autographs that the distribution of lewisite is somewhat different than was noted with mustard. The labeled material is deposited primarily in the hair and hair follicles, with a smaller amount in the epidermis. Sebaceous glands and deeper structures of the skin, such as muscle, blood vessels, and corium, appear to accumulate negligible amounts of the labeled material as compared with hair and hair follicles.

The section in Figure 8 was taken from a sample of tissue to which the lewisite had been applied for a period of 15 minutes before being washed off. In the radio-autograph in Figure 8, the bulk of the activity appears to be concentrated in the hair follicles and shaft with very little present in the epidermis, a very faint wavy line indicating the accumulation of a small amount in the epidermis. The left-hand corner of the section in Figure 8 reveals a hair follicle and developing hair lying obliquely; the corresponding radio-autograph indicates that a

small amount of material was accumulated in the central portion of the follicle which, presumably, is occupied by the shaft of the hair. Figure 9 was taken from a section of tissue on which lewisite had been allowed to remain for 1 hour before its removal. The general appearance of the radio-autograph is similar to that noted for the 15 minute exposures, in that the bulk of the labeled material appears to be concentrated in the epidermis, hair, and hair follicles. Figure 9 reveals a deposition of the labeled material very clearly in the epidermal layer. The hair follicle in the center of the section apparently contained a very large amount of radio-arsenic, and, as a result, the radio-autograph gives a very dark blur. The follicles lying deeper in the sections have also apparently accumulated an appreciable amount of radio-arsenic.

Studies of Rabbit Eyes Exposed to Mustard Gas

Two experiments were done on rabbit eyes. In the first, liquid mustard was placed directly on the eye; in the second, the eye was subjected to the vapor by placing a small cup containing the material over the eye. The experiments were done at room temperature. Essentially similar results were obtained in both experiments, although the histologic preparations in the latter experiment were better and the interpretation of the radio-autographs thus facilitated. The results given here are based on the vapor-exposed eyes.

Figure 10 represents a 5 minute exposure to mustard, the eye having been removed immediately after exposure. The length of time required to bring out the small amount of activity in the lens and iris resulted in a loss in definition and gradient in the cornea. Figure 11 also represents a 5 minute exposure, but in this experiment the eye was not removed until the seventh day after exposure. It may be significant that the proportionate amount of activity present in the iris is greatly reduced in this case. This suggests the possibility that at least a portion of the activity shown in the iris (Figs. 10 and 11) may not represent fixed mustard but merely mustard or one of its derivatives which normally may pass through the iris into the blood stream. The alternative explanation that the mustard becomes "unfixed" more rapidly from iris tissue than from corneal tissue does not appear attractive.

Comparative Studies of Unfixed and Formalin-Fixed Tissues

For purposes of comparison with the results obtained from the formalin-fixed material and to rule out the possibility of migration of the two gases, radio-autographs were made from frozen, unfixed pig skin and human skin. These radio-autographs presented no significant

differences in appearance as compared to the radio-autographs from formalin-fixed sections.

Determination of Radio-Activity in Small Regions of Tissue Sections by Measuring the Darkening of the Photographic Films of Radio-Autographs

Through the technic of radio-autography, the deposition of a radio-active element in a tissue can be correlated with histologic structure. The radio-activity in a tissue as a whole can be easily measured by one of various counting devices, *i.e.*, Geiger counter, electroscope. On the other hand, the determination of the radio-activity of an individual structure has heretofore been extremely difficult. A method for determining the amount of activity in specific histologic structures has been worked out.

The degree of darkening of a radio-autograph is dependent upon the uptake of the radio-active element by the particular structure concerned. Since the darkening of photographic film can be measured by microphotometer tracings, it should be possible to determine the activity in a structure from the degree of darkening in the radio-autograph if standards of known activity producing a uniform darkening can be prepared for comparison. Since the radio-activity per mg. of mustard is known, the actual quantity of mustard in the histologic unit can be calculated assuming that the radio-active sulfur (S^*) atoms are still incorporated in the mustard molecules.

Standards, using BaS^*O_4, were prepared with shellac as a base for the radio-active salt. The following method was used:

(1) Solid BaS^*O_4 was mixed with thin shellac (about 1 mg. per cc. of shellac).

(2) The mixture was spread on glass slides with an oil paintbrush.

(3) To determine the uniformity of distribution of the BaS^*O_4, each slide was covered with photographic film, wrapped in black paper, and the package placed under a lead weight to hold the film in close contact with the slide. After 18 hours, the film was developed. Uniform areas of darkening were delineated by placing metal tubing of 1 cm. in outer diameter in the area and the remainder of the shellac on the slide scraped off. Agfa no-screen x-ray was used in these experiments; development was standardized at $2\frac{1}{2}$ minutes at 21°C. in Eastman concentrated x-ray developer diluted 1:4.

(4) The activity of each sample was counted with a Geiger counter before exposure to the film. The film was exposed to samples for varying time intervals so that different degrees of darkening would be obtained. To determine the degree of darkening, or density, micropho-

tometer tracings were made of each film exposure. The following equation was used to express density:

$$D = \log_{10} \frac{i_0}{i}, \text{ where } i_0 = \text{incident light, and } i = \text{transmitted light}$$

(5) Text-Figure 1 indicates graphically the relationship between the density and the total number of beta particles emitted by the
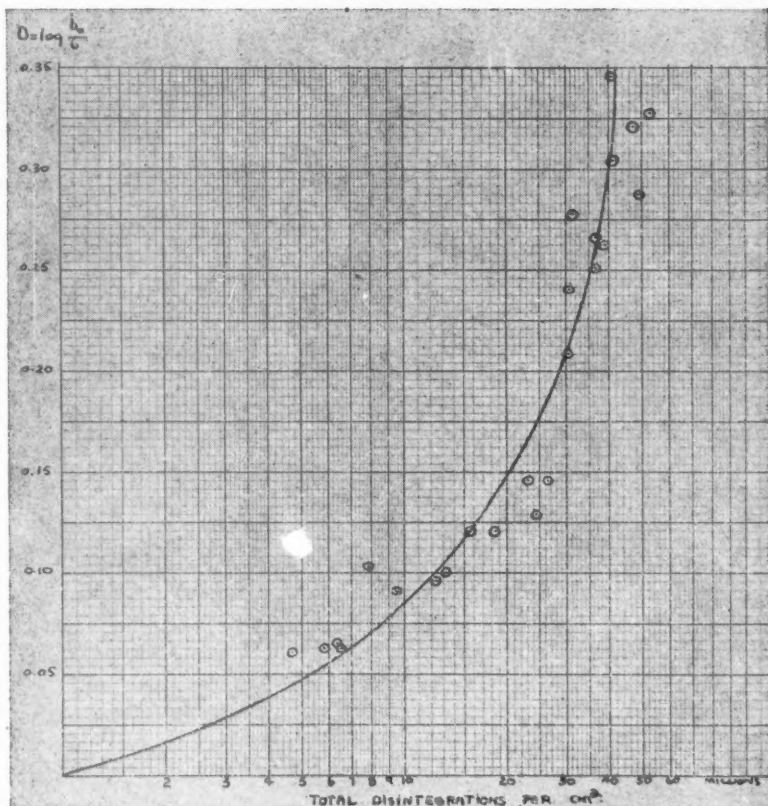
Text-Figure 1. Relationship between density of photographic blackening and the total number of disintegrations emitted by the sample.

sample. Corrections for the efficiency of the counter, decay of the radio-sulfur, and self-absorption of the beta particles from the radio-sulfur in the shellac film were made. It must be noted that the number of particles hitting the emulsion is only half of the total number of disintegrations minus those accounted for by self-absorption.

(6) Differences in the character of the emulsion, development, and in agitation during film development must be carefully controlled.

It is possible from the above data to estimate the quantity of radio-sulfur in a thin sample of radio-active material. This offers the possibility of employing microphotometric methods for measuring the darkening of film to determine the radio-activity present in small regions such as epidermis, hair follicles, sebaceous glands and blood vessels, thus leading to an estimate of the mustard content of a histologic unit. This interpretation assumes that radio-sulfur in the tissue is in the form of mustard and has not been split off and converted into other compounds. This procedure, is, of course, applicable to other radio-elements, but the calibration described in the above experiment would have to be repeated for the radio-element in question. This is due to the fact that the energies of the beta radiations differ for each radio-element, and the degree of darkening of the photographic emulsion varies with the energy of the radiation.

An experiment of this type can be illustrated as follows. A microphotometric tracing was made of the blood vessel located 3 cm. from the bottom of the photomicrograph in Figure 5. The density was found to correspond to a total number of disintegrations of approximately 20 million per square cm. The film was exposed to the tissue section for 14 days; thus the average, approximate activity in the blood vessel was 17 disintegrations per second during the interval in which the autograph was made.

The content of radio-sulfur per mg. of mustard was approximately 5 microcuries at the time the radio-autograph was made. This is equivalent to 1.9×10^5 disintegrations per second per mg. of mustard. Thus, 0.1 μg. of mustard was present in the 10 μ section of the blood vessel, the volume of the latter being 7×10^{-5} cmm., or, in other words, 14 mg. of mustard was present per gm. of blood vessel.

The tissue was exposed in such a manner that 1 mg. penetrated each square cm. of tissue. Of this 1 mg., about 250 μg. was fixed per square cm. of tissue, and 70 per cent of this fixed material was in the epidermis, which was 70 μ thick; thus the average mustard content of epidermis was 25 mg. per gm. Thirty per cent of the fixed material was in the corium, which is about 1.5 to 2 mm. thick; thus, the average mustard content of the corium was 0.37 mg. per gm.

Summary and Conclusions

The distribution of two war gases, mustard and lewisite, labeled with radio-active sulfur (S^{35}) and radio-active arsenic (As^{74}), respectively, in skin and eye tissues has been studied using the radio-autographic technic.

In human skin, lewisite was found to be fixed primarily in the epidermis, with very small amounts found in the dermis. The lewisite present in the dermis was found in some blood vessels, in regions of the perivascular exudate, in some hair follicles, and in one case in a sebaceous gland. There was massive necrosis of most of the epidermal layer and corium resultant from the lewisite.

Comparable studies with mustard gas applied on human skin showed this material to be fixed in epidermis and dermis. The blackening of the autographs was so great, due to the accumulation of mustard, that it was impossible to determine the specific concentration by blood vessels; hair follicles were seen so rarely that it was difficult to determine whether or not they fixed mustard. The marked degree of necrosis noted with lewisite gas was not apparent with the mustard gas; this may be explained by the fact that injury by mustard is not detectable within 24 hours, whereas the effect of lewisite is more rapid and necrotic effects are visible within a much shorter time.

A long exposure of pig skin to mustard (6 hours to 2 mg.) showed a high concentration in epidermis, dermis, hair follicles and adjacent sebaceous glands, and blood vessels. A small amount was found in the hypodermis in the bands of fibrous tissue surrounding fatty tissue, and also in deep blood vessels.

Shorter exposures of pig skin to mustard gas (15 minutes to 475 μg.) showed concentration in epidermis, dermis, and hair follicles.

Short exposures of pig skin to lewisite (15 minutes to 1.269 mg., and 1 hour to 1.534 mg.) showed concentration primarily in hair, superficially located hair follicles, and a very small amount in epidermis.

In all of the autographs, mustard gas penetrated the skin much more deeply than lewisite with a corresponding exposure. This deep penetration could explain the great destruction and deep burns resultant from exposure to mustard gas. In both the mustard and lewisite studies an accumulation of these two materials was noted in and around blood vessels. With destruction of blood vessels and subsequent local anemia one would expect slow healing of the affected skin area to ensue, which is a characteristic feature of these burns.

In rabbit eyes exposed to mustard gas this material was fixed primarily in the cornea, with a small amount in the conjunctiva, and a very small amount in the iris and lens.

By the method described it is possible to determine the radio-activity present in small regions of tissue sections, i.e., in blood vessels, hairs, hair follicles and accessory glands of the skin.

Ophthalmology, Harvard Medical School, with the eye studies; the generous cooperation of Dr. F. C. Henriques, Jr., and co-workers of the Gibbs Laboratory, Harvard University, in making available to us radio-active mustard and lewisite gas, and exposed skin.

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DESCRIPTION OF PLATES

PLATE 62

FIG. 1. Human skin exposed for 10 minutes to 475 µg. of mustard, tissue excised 24 hours after application. Fixation of mustard occurs in epidermis and corium. × 26.

FIG. 2. Human skin exposed for 15 minutes to 475 µg. of lewisite, tissue excised 24 hours after application. Fixation occurs primarily in epidermis, hair follicles (at extreme left of photomicrograph), and in an associated sebaceous gland (below follicles). The smaller squared area shows a blood vessel which has accumulated a small amount of activity. × 26.

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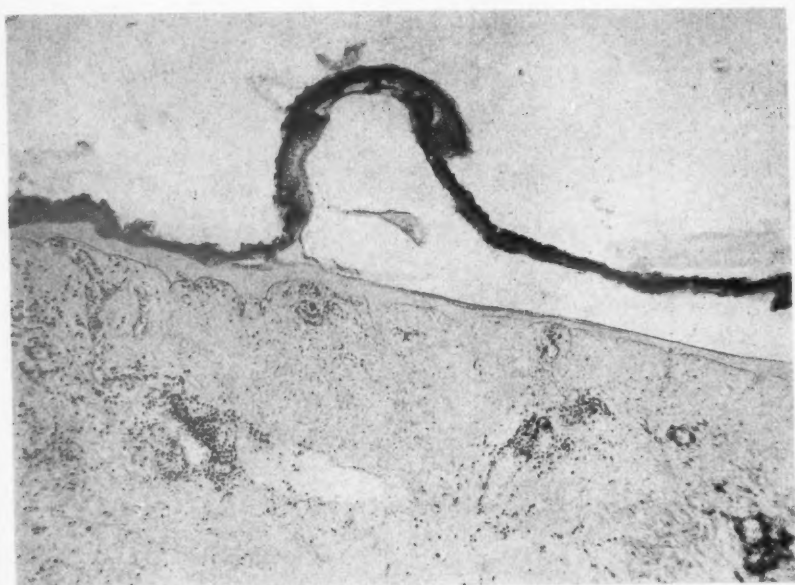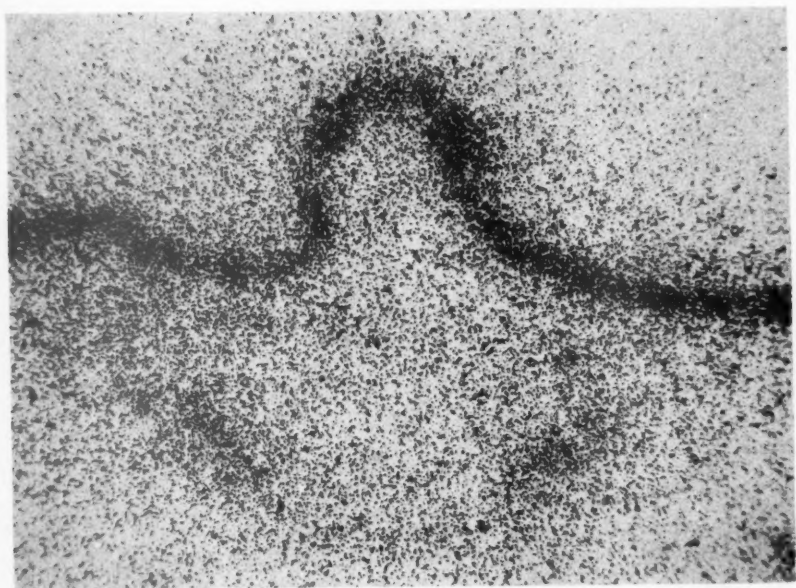th
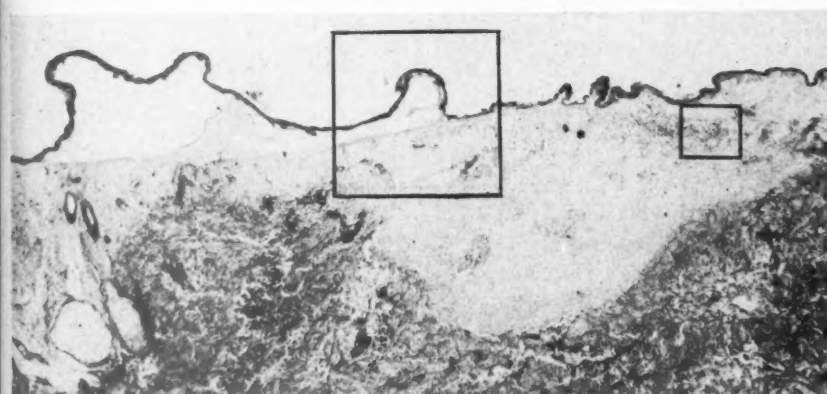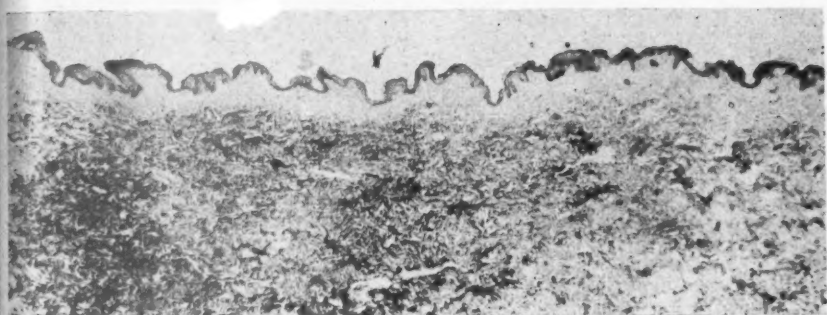
Fig. 3. Human skin exposed to lewisite. Higher magnification of the larger squared area seen in Figure 2. Lewisite fixation occurs in the perivascular infiltration around blood vessels and in the epidermis separated from the papillary layer. × 100.
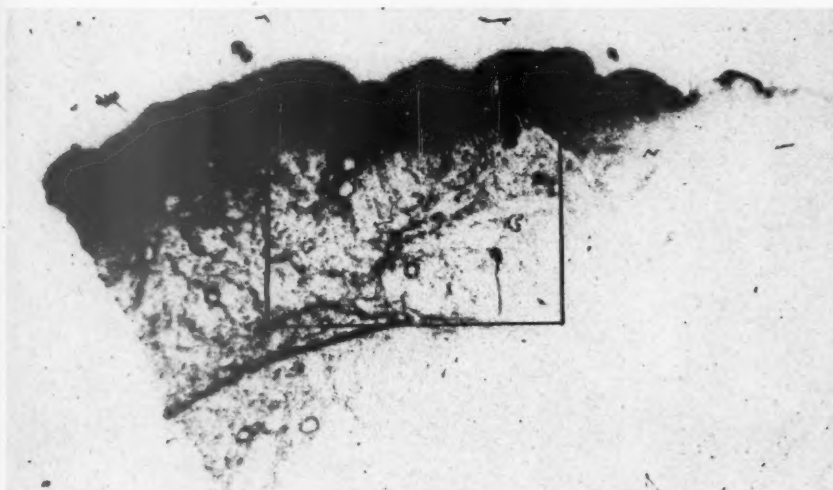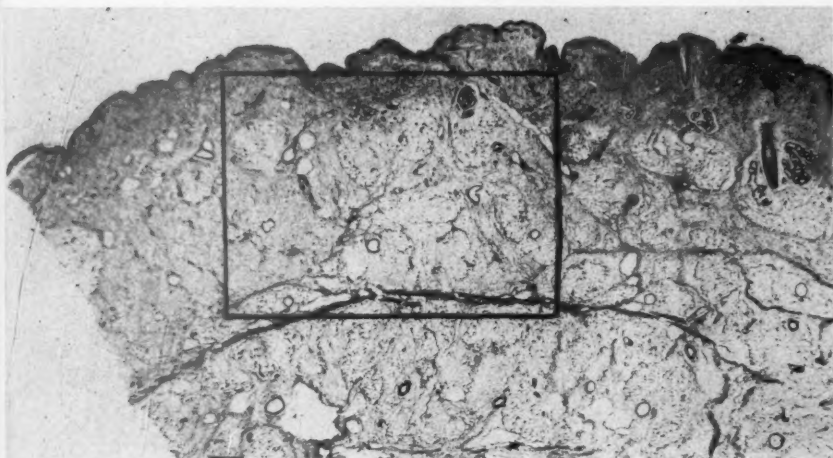
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Axelrod and Hamilton

Lewisite and Mustard Gas in Skin and Eye

FIG. 4. Pig skin exposed for 6 hours to 2 mg. of mustard and excised 24 hours after application. A large amount of mustard is fixed in the epidermis, corium, blood vessels, sebaceous glands, hair follicles, and subcutaneous fibrous tissues. × 10.

4

FIG. 5. Pig skin exposed to mustard gas. Higher magnification of the squared area marked on Figure 4. Sebaceous glands (upper right), subcutaneous fibrous tissue (lower left), and blood vessels are seen to accumulate large amounts of mustard. ✕ 30.
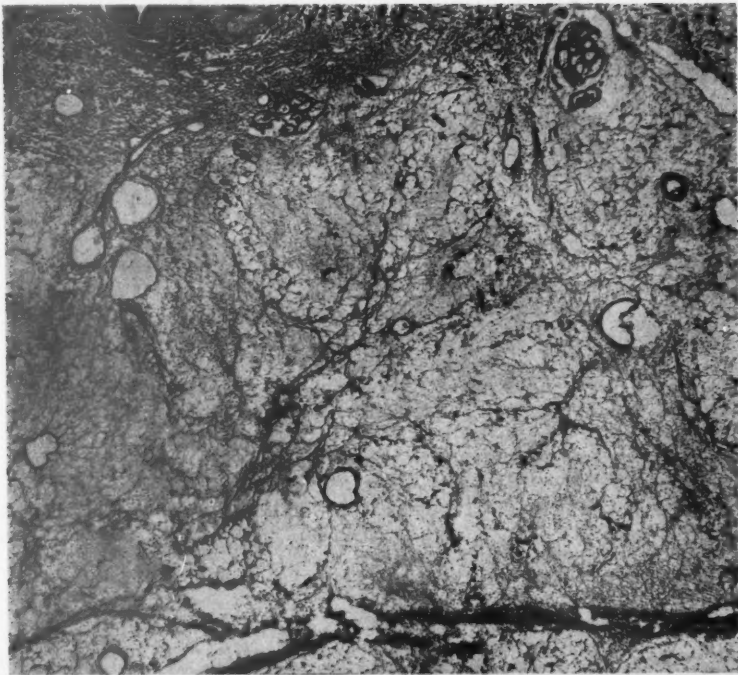
Fig. 6. Pig skin exposed for 15 minutes to 475 µg. of mustard gas; tissue immediately excised. Most of the mustard fixation occurred in the epidermis, with negligible amounts extending into the papillary layer of the dermis. Superficially located hair follicles contained mustard. × 5.

Fig. 7. Pig skin exposed for 15 minutes to 475 µg. of mustard gas; tissue excised 24 hours later. Mustard has penetrated into the dermis, and is concentrated in deep-lying hair follicles. × 5.

6

7

Axe

PLATE 67

FIG. 8. Pig skin exposed to 1.269 mg. of lewisite for 15 minutes; excision 24 hours later. The bulk of the lewisite is accumulated in hair follicles and hairs with smaller amounts in the epidermis. × 20.

FIG. 9. Pig skin exposed to 1.534 mg. of lewisite for 1 hour; excision 24 hours later. Lewisite has accumulated in hair, hair follicles, and epidermis. × 20.

8

9

PLATE 67

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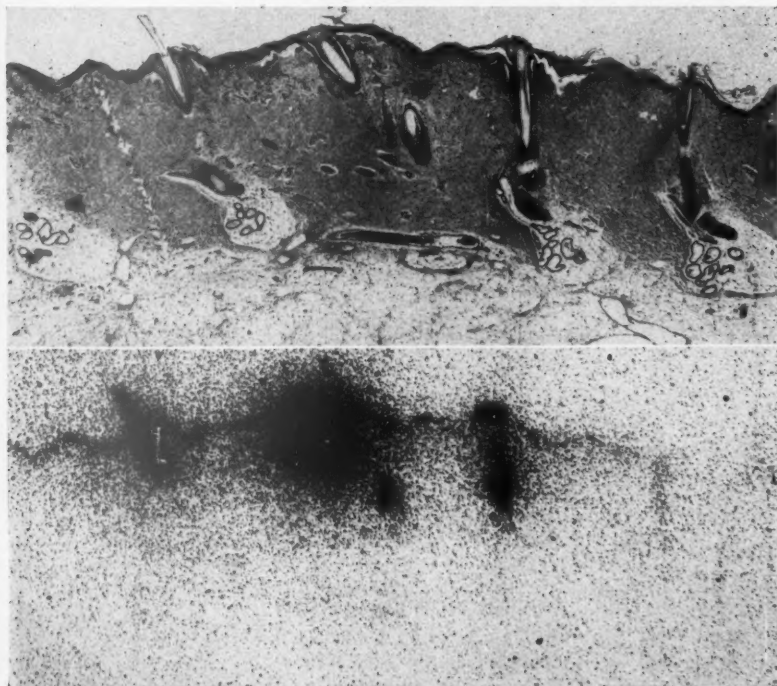
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Axelrod and Hamilton

Lewisite and Mustard Gas in Skin and Eye
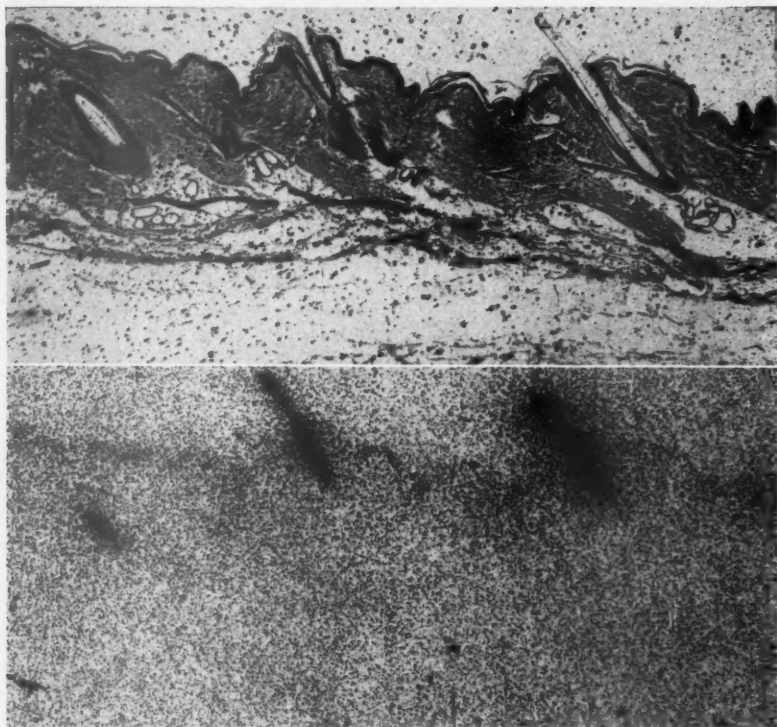
Fig. 10. Rabbit eye removed immediately after a 5 minute exposure to mustard vapor. Fixation is primarily in the cornea, with the iris, lens, and conjunctiva containing a lesser amount of activity. $\times$ 5.
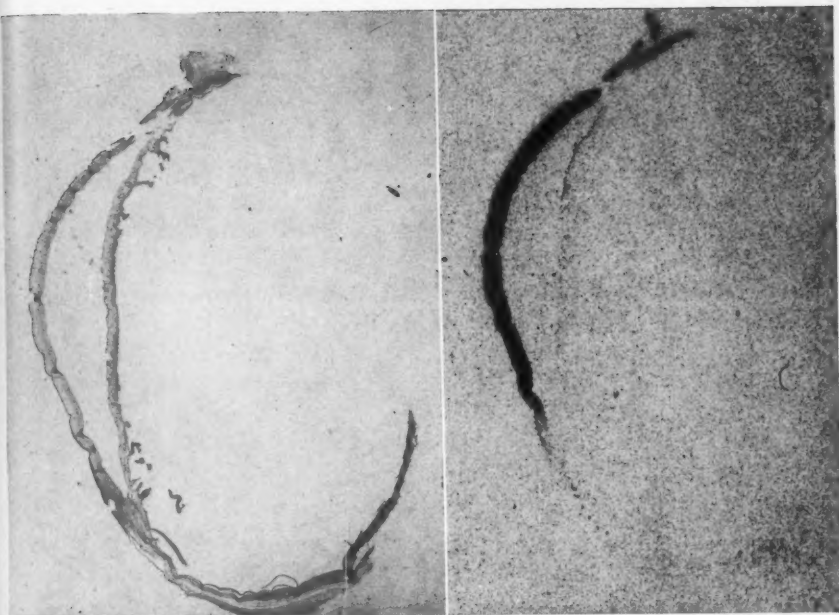
Fig. 11. Rabbit eye removed 7 days after a 5 minute exposure to mustard. Fixation of mustard is primarily in the cornea. $\times$ 5.

PLATE 85

11

10

Lewisite and Mustard Gas in Skin and Eye

Axelrod and Hamilton

SO-CALLED PULMONARY ADENOMATOSIS AND "ALVEOLAR CELL TUMORS"

REPORT OF A CASE *

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There occurs in man a relatively uncommon disease, so-called pulmonary adenomatosis, which bears a remarkable resemblance to an epizootic disease of sheep known variously as jaagsiekte, epizootic adenomatosis, pulmonary adenomatosis, verminous pneumonia, and Montana progressive pneumonia of sheep. This disease in sheep, which has been thoroughly described by Mitchell,[1] Dungal,[2] and Cowdry,[3] is characterized by marked inflammatory changes in the lung associated with an irregular proliferation of cells lining the alveoli. These cells adhere to the alveolar walls and, indeed, appear to arise from them. Such lining cells which histologically are epithelial in appearance vary from cuboidal to columnar, are not ciliated, show papillary infolding into the alveoli, and apparently are not continuous with bronchiolar epithelium. When fully developed the microscopic picture resembles an adenoma or adenocarcinoma but the cells are regular and metastases do not occur.[†]

In 1907 Helly[4] described an unusual tumor in man which resembles the condition found in sheep. Since that time 10 additional and "acceptable" cases occurring in man have been reported respectively by Löhlein,[5] Oberndorfer,[6] Bonne,[7] Richardson,[8] Breise,[9] Sims,[10] Bell,[11] Taft and Nickerson [12] (2 cases), and Wood and Pierson.[13] In all cases except one [13] the diagnosis was established at autopsy, as was true in the case reported here.

REPORT OF CASE

The patient was a white Jewish housewife, 70 years old, who was admitted to the medical service of Dr. David Mendel at about 10:30 a.m. on June 9, 1945, critically ill. The history, obtained from a daughter, stated that 7 weeks prior to admission the patient began to cough violently and to expectorate thick sputum which contained no blood. The coughing continued at night. During the week previous to admission the daughter had noted progressive dyspnea and orthopnea, and slight cyanosis. A general feeling of malaise and headache accompanied this condition. The past history revealed that the patient had had an attack of "bronchitis" the previous summer from which she apparently recovered. Otherwise, the past history and family history contained nothing contributing to knowledge of the present illness.

Physical examination revealed an emaciated, poorly developed patient showing moderate dyspnea and mild cyanosis of mucous membranes and nail beds. There

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† One exception by Aynaud, Peyron, and Falchetti, cited by Dungal.[2]

was dullness to percussion of both lung fields extending almost to the apices. Breath sounds could not be heard and moist, coarse, and bubbling râles were heard throughout the lungs. Heart sounds could not be heard due to the râles and the blood pressure was 150/75 mm. Hg. Other physical findings were within normal limits. The temperature, on admission, was 98.6°F.; pulse, 108 per minute; respiration, 42 per minute.

Within ½ hour after admission, the patient was placed in an oxygen tent and given coramine intravenously. Her respirations were labored. She was drowsy and took fluids very poorly. On the afternoon of admission, an electrocardiogram showed slight left axis deviation. A portable roentgenogram of the chest showed marked obscuration of both lung fields extending upwards to the level of the second rib anteriorly on the right and to the third rib anteriorly on the left. Both diaphragms and the cardiac silhouette were completely obscured. A small, translucent area in the left lower chest close to the outer aspect was noted.

Twenty-four hours after admission thoracentesis was attempted but no fluid could be aspirated. The patient's condition did not permit further laboratory studies. She died suddenly in the oxygen tent, 29 hours after admission.

The clinical diagnosis was pneumonitis, atypical, with bilateral pleural effusion.

POST-MORTEM FINDINGS

Autopsy was performed 17 hours after death.

The body was that of an emaciated, poorly developed adult white female, 70 years of age. Scarcely any recognizable subcutaneous fat was present. The right thoracic cavity was partially obliterated by dense, sheet-like adhesions which bound the lung in multiple areas to the chest wall. Where adhesions were not present, a fine deposit of granular, yellowish gray fibrin was noted on the pleural surfaces. On the left, similar but less extensive adhesions were present and the pleural surface of the left upper lobe contained a fine deposit of granular fibrin. The left lower lobe was small and collapsed, lay in a posterior position, and was flabby and almost cyst-like to palpation.

The upper third of the left upper lobe was crepitant and cottony in consistency, as was the lowermost portion of the left upper lobe. In the mid-portion of this lobe an irregular band of consolidated tissue was palpable. This band measured 8 cm. in width. Section revealed the upper and lower one-thirds of this lobe to be red and spongy while the middle one-third was gray, consolidated, slightly elevated, granular, and sticky (Fig. 1). Culture from this area yielded Friedländer's bacillus. The left lower lobe was small, violet in color, and collapsed like a bag when placed upon the table. Section revealed this entire lobe to consist of an irregularly loculated and trabeculated cavity 7 by 5 cm. in diameter. The wall of the cavity measured 2 to 3 mm. in thickness and it contained a small amount of yellowish gray, sticky, mucopurulent exudate. The bronchus to the left lower lobe communicated directly with this cavity and no alteration of the bronchial wall was noted.

On the right, all lobes were consolidated and noncrepitant. Section through all lobes revealed the major portion of each to consist of gray, granular, elevated, consolidated, noncrepitant tissue from which a considerable amount of sticky, yellowish gray exudate could be scraped. Culture from these lobes yielded Friedländer's bacillus and the gross appearance was that of lobar pneumonia in the stage of gray hepatization. No nodules of any type were present.

The major bronchi were filled with a large amount of sticky, yellowish gray, mucopurulent material. The mucous membranes were hyperemic but otherwise unaltered. The mediastinal lymph nodes were slightly enlarged and on section showed a mottled gray and black, homogeneous, moist surface. No tumor nodules of any type were present.

The balance of the gross examination failed to show any evidence of disease directly related to the lung condition other than cloudy swelling of the parenchymatous organs. There was generalized arteriosclerosis. A hemangioma of the liver and cystitis were present.

To summarize, the gross findings in the lungs were indistinguishable from ordinary pneumonia due to Friedländer's bacillus or Type III pneumococcus and of essentially lobar distribution, with an extensive remote abscess of the left lower lobe.

Microscopic Findings

Multiple sections taken from all lobes on the right revealed the majority of alveoli to be filled with large numbers of polymorphonuclear leukocytes, variable amounts of fibrin, and large numbers of pale, circular, phagocytic cells containing abundant, finely foamy cytoplasm and relatively small, dense, eccentrically placed nuclei (Fig. 2). Innumerable alveoli were lined either completely or partially by single and at times pseudostratified layers of remarkably tall-columnar epithelial cells (Fig. 3). These cells contained abundant, foamy cytoplasm staining pale pink with eosin and showed numerous goblet formations (Fig. 4) and brush borders of the free edge (Fig. 5). No cilia could be identified. The nuclei of these cells were oval, somewhat vesicular in character, and occasionally contained prominent nuclei. In many situations cells were apposed to the alveolar wall and, indeed, appeared to arise from the alveolus proper. In others these cells had become detached from alveolar walls and lay within alveolar lumina. Papillary infolding of these cells was a common occurrence. Only an occasional mitotic figure was encountered and the cells were remarkably uniform in size, shape, and staining quality.

The distribution of abnormally lined alveoli was quite irregular

throughout all sections (Fig. 6). Areas were encountered where prac-
tically all alveoli were lined by these cells, and in other fields there
were no lining cells. No invasion of lymphatic or vascular spaces or of
the pleura had occurred, although alveoli lying immediately adjacent
to the pleura were lined by such cells.

Sections through the left upper lobe showed essentially the same pic-
ture as that seen in all lobes on the right. Sections taken through the
thin wall of the cystic left lower lobe showed a trabeculated wall of
condensed, anthracotic fibrous connective tissue diffusely infiltrated by
lymphocytes and containing many thick-walled blood vessels. An oc-
casional alveolus still remained and was lined by tall-columnar cells
similar to those described above.

Sections through multiple hilar lymph nodes failed to reveal evi-
dence of metastases, and the balance of the microscopic examination of
organs failed to reveal changes relating to the pulmonary lesion.

DISCUSSION

From a clinical point of view, as far as can be determined, there are
no pathognomonic signs, symptoms (except dyspnea), or roentgenologic
appearances which would enable the clinician to make the ante-mortem
diagnosis of pulmonary adenomatosis with any degree of certainty.
The majority of these cases reported in the literature have been vari-
ously diagnosed clinically as pneumonia or tuberculosis, and, in some
cases, tumors have been suspected. In the present case a clinical diag-
nosis of atypical pneumonia with abscess formation was made.

The gross appearance of the lungs in cases of human pulmonary
adenomatosis has been described as resembling noncaseating miliary
tuberculosis,[13] nodular and consolidated; [10] but in most cases has re-
sembled lobar pneumonia in the stage of gray hepatization.[11,12] In none
of the reported cases has any bronchial or bronchiolar lesion suggesting
primary bronchiogenic carcinoma been described. In the cases of Taft
and Nickerson [12] and in the present instance a considerable amount of
sticky, gelatinous exudate could be scraped from the cut surface, sug-
gesting a Friedländer's bacillus pneumonia.

Microscopically, the picture described by all authors is remarkably
uniform, varying only with the degree of inflammatory change and ex-
tent of adenomatosis present. Irregularly scattered, large, diffusely
involved areas show alveoli which are lined by either regular tall-colum-
nar or high-cuboidal, nonciliated epithelial cells. These cells are re-
markably uniform in size, shape, and staining quality and only rare
mitotic figures are encountered. The nuclei of these cells are, for the
most part, basally arranged, but at times lie in the midportion of the

cells. The chromatin in the nuclei is coarse and occasional nucleoli are noted. The cytoplasm of these lining cells is eosinophilic, reveals goblet formation and is slightly granular, and at times exhibits a brush border. These lining cells do not resemble the ciliated cells of bronchioles and, indeed, are not continuous with them. The hyperplastic epithelial cells rest upon apparently unaltered or, at times, minimally thickened, alveolar walls and frequently project in papillary folds into the lumina of alveoli. Desquamation of these cells in single-celled sheets is not uncommon and it would appear that these cells are very delicately attached to the alveolar walls. There is no destruction of alveolar walls and no lymphatic invasion is noted. Occasional mononuclear phagocytes with finely foamy cytoplasm are seen within alveoli and the amount and character of the exudate within alveoli are variable.

Attempts to stain for mucin in the present case were uniformly unsuccessful, but Taft and Nickerson [12] noted mucin which stained with aniline dyes.

The similarity between human pulmonary adenomatosis and the lesions occurring in sheep raises a number of interesting speculations. While no specific etiologic agent has been proved as the cause of jaagsiekte in sheep, the work of Dungal, Gislason, and Taylor [14] strongly suggests that the disease is infectious and communicable. A virus has been suggested by Cowdry,[3] Bonne,[7] and Bell,[11] but attempts to demonstrate a causative agent and/or to transmit the disease to laboratory animals have been unsuccessful. Amongst sheep, however, the transmission can easily be effected by housing sheep together with one or more diseased animals. In only one instance were Dungal, Gislason, and Taylor able to transmit the disease from one sheep to another by intrapulmonary inoculation. There is, at present, no evidence to suggest that pulmonary adenomatosis in man is of an infectious or communicable nature, but it must be remembered that too few observations have as yet been made to draw any conclusions. Attempts to transmit the disease to various laboratory animals from human autopsy material by Richardson,[8] Sims,[10] and Wood and Pierson [13] have been uniformly unsuccessful.

Another interesting problem which pulmonary adenomatosis raises is the controversial question regarding the presence and nature of alveolar lining cells. On the one hand, Bensley and Bensley,[15] Miller,[16] and Cooper [17] have maintained that a continuous layer of epithelial cells line the alveoli, while Maximow and Bloom,[18] Rose,[19] Fried,[20] and Loosli [21] have stated that the lining cells are mesenchymal. Ross [22] believes that both mesenchymal and epithelial cells line alveoli. While this complex problem remains to be settled definitively, the fact that the

cells lining the alveoli in human pulmonary adenomatosis appear to be multicentric in origin, appear to spring *de novo* from the alveolar walls, and are nonciliated and noncontinuous with the bronchiolar epithelium strongly suggests that cells do line alveoli either completely or incompletely. It is certain that in pulmonary adenomatosis these cells are of an epithelial nature. Whether these proliferating cells spring from pre-existing epithelial cells or represent metaplasia from an indifferent type of cell under varying pathologic conditions is difficult to state categorically. Oberndorfer,[6] Bell,[11] and Taft and Nickerson [12] believe these cells have an epithelial origin, and Bell believes that occasional epithelial lining cells may be found in post-natal lungs. Herbut [23] has attempted to demonstrate that the epithelial cells lining the alveoli are derived from bronchiolar epithelium. This concept does not account for the distinctly different appearance of the tall, nonciliated epithelial cells of pulmonary adenomatosis from that of the relatively low ciliated cells lining the bronchioles. Furthermore, since widespread bilateral pulmonary adenomatosis without lymphatic invasion does occur, the concept that this arises on the basis of metaplasia from bronchiectatic foci seems unlikely. In none of the reported cases, as in the present case, was bronchiectasis a feature. Geever, Neubuerger, and Davis,[24] on the other hand, while recognizing the presence of epithelium-like septal cells, refused to commit themselves as to the nature of the cell and referred to tumors arising from these cells as "alveolar cell" tumors. However, Helly's [4] opinion that the cells arise from alveolar duct epithelium cannot be entirely dismissed.

The question whether human pulmonary adenomatosis, as the name suggests, is an entirely benign, hyperplastic (*i.e.*, nonmetastasizing) process or whether it may be the initiating point for some of the so-called alveolar tumors described and collected by Neubuerger and Geever [25] is of considerable importance. Of the 12 "acceptable" cases (including the one reported here), only those of Oberndorfer [6] and Breise [9] showed metastases to lymph nodes. All other cases not only appeared to be benign from a histologic standpoint but failed to show metastases. The only instance of metastasis in jaagsiekte of sheep appears to be that of Aynaud, Peyron, and Falchetti (cited by Dungal [2]) in which a metastasis was found in a regional peribronchial lymph node. It appears, therefore, that occasional cases of jaagsiekte and pulmonary adenomatosis may, and indeed do, metastasize, thus fulfilling all the criteria of a malignant neoplasm.

In no instance in the reported cases of pulmonary adenomatosis has there been demonstrated a primary bronchial focus which would fulfill the recognized criteria. The fact that the disease is usually bilateral

without any histologic evidence of lymphatic invasion strongly suggests that it is multicentric in origin. Under these circumstances, it seems reasonable to regard pulmonary adenomatosis as a well differentiated, relatively slowly growing but eventually metastasizing pulmonary tumor of an unusual type which differs in the details mentioned above from the ordinary bronchiogenic carcinoma.

Neubuerger and Geever [25] collected from the literature 43 cases of unusual tumors of the lung to which they gave the name "alveolar cell tumors" in order to avoid controversy as to the histogenesis of the cells. Included in this group are the "acceptable" cases of so-called pulmonary adenomatosis of Helly,[4] Löhlein,[5] Oberndorfer,[6] Bonne,[7] Richardson,[8] and Breise.[9] These cases differ in no significant respects from the remainder of the 43 collected cases, all of which showed a pathologic change indistinguishable from pulmonary adenomatosis. Of these 43 cases, 24 (or 56 per cent) showed metastases. All of the collected cases of Neubuerger and Geever, whether controversial or otherwise, in their opinion, showed characteristic cuboidal to columnar epithelial cells with or without papillary infolded lining alveoli, and in all cases the usual bronchiogenic origin was excluded. No evidence that the lung lesions were metastatic in nature was present. In 1945 Geever, Carter, Neubuerger, and Schmidt [26] reported 6 additional cases of "alveolar cell" tumor. In 4 of these, metastases were present and showed characteristic cuboidal or columnar cells lining alveoli; in all, the usual bronchiogenic type of tumor was excluded.

It would seem, therefore, that pulmonary adenomatosis and "alveolar cell" tumors are, from a cytologic point of view, identical and that the presence and extent of metastases are variable. It may well be that the degree of pneumonia which usually accompanies this disease in both sheep and man may cause death before metastases develop.

SUMMARY

A case of histologically benign pulmonary adenomatosis without metastases forms the basis of this report. This condition is similar to the epizootic disease of sheep. In occasional cases of jaagsiekte and of pulmonary adenomatosis metastasis has occurred.

Cytologically, the cases of so-called pulmonary adenomatosis appear to be identical with a much larger series of collected and reported cases which have been termed "alveolar cell" tumors, about half of which metastasize.

Pulmonary adenomatosis and alveolar cell tumors may be regarded as unusual forms of pulmonary carcinoma presumably arising from alveolar lining cells.

Since this paper was submitted for publication, Dungal (*Am. J. Path.*, 1946, **22**, 737–759) has reported upon his experiences with experimental jaagsiekte. He concluded that jaagsiekte is due to a pneumotropic virus strictly limited to the lungs and bronchi of sheep and excreted with the respiratory air. He stated that no cases of pulmonary adenomatosis have appeared among shepherds who are in contact with sick sheep for long periods of time and he therefore believes that man is immune to this particular virus.

Also, since submitting this paper, I have had an opportunity to study by autopsy an additional case of "alveolar cell" tumor of the lungs. In this case the lesions in the lungs are identical with those reported. No metastases were present in the broncho-pulmonary or mediastinal lymph nodes but metastases were found in the brain. This study emphasizes the belief that pulmonary adenomatosis and "alveolar cell" carcinomas of the lung are probably identical.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 69

FIG. 1. Left lung showing the character of the cut surface of the midportion of the left upper lobe. The left lower lobe contains the collapsed, cystic, remote abscess seen at the left.

FIG. 2. Pneumonic exudate consisting of fibrin, mucus, and large phagocytic cells with finely foamy cytoplasm as well as lymphocytes and rare polymorphonuclear leukocytes. Of note are the desquamated lining cells in the center of the field and the cuboidal cells lining the alveolar septa. Hematoxylin and eosin stain. × 215.

PLATE 69
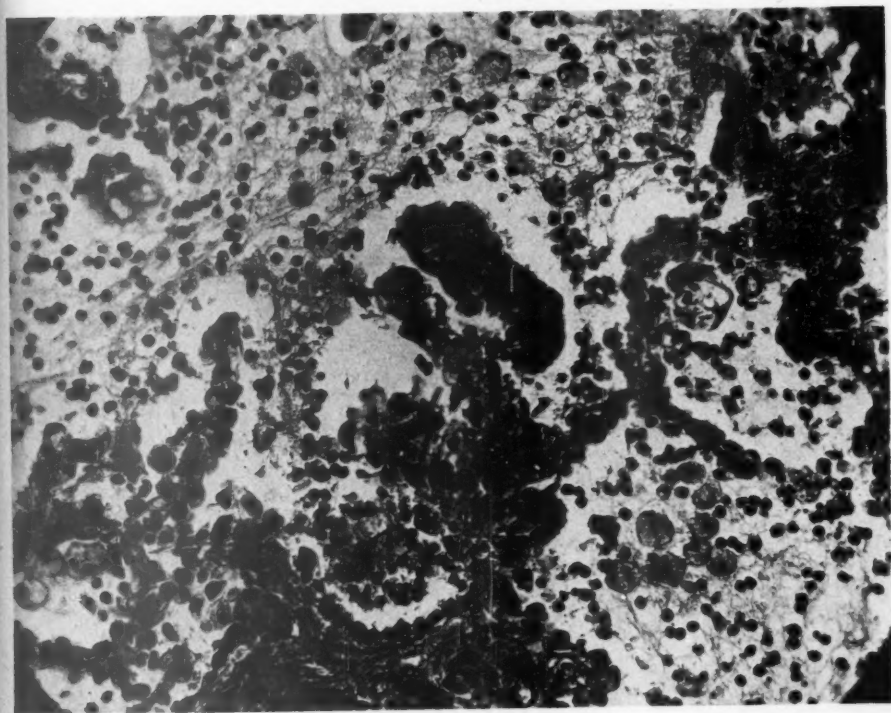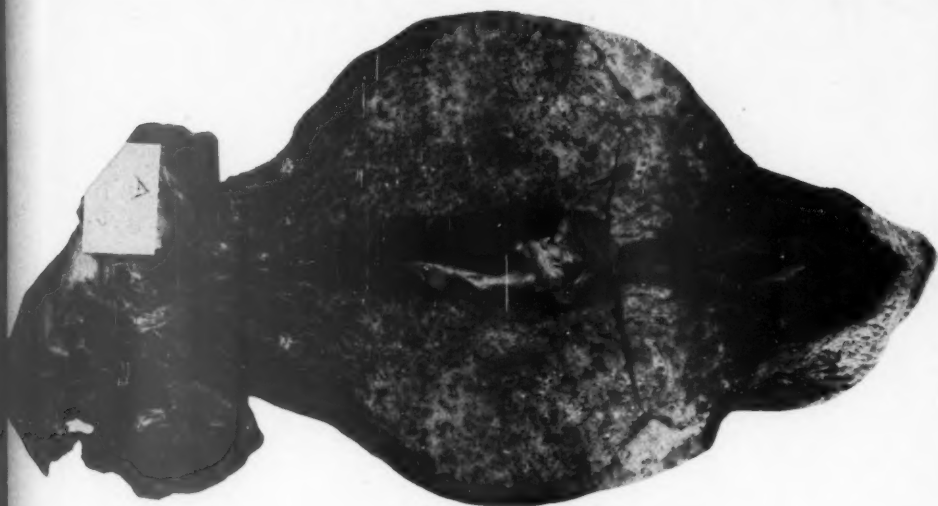
Simon   Pulmonary Adenomatosis

FIG. 3. Appearance of alveoli lined by tall-columnar cells showing papillary infolding and goblet cells. Alveolar walls are thin, delicate, and unaltered. Hematoxylin and eosin stain. $\times$ 115.

FIG. 4. This photomicrograph demonstrates the delicate attachment of lining cells to the unaltered alveolar walls, together with the tendency toward detachment and desquamation of the cells into the lumen. Goblet formation is well seen here. Hematoxylin and eosin stain. $\times$ 210.
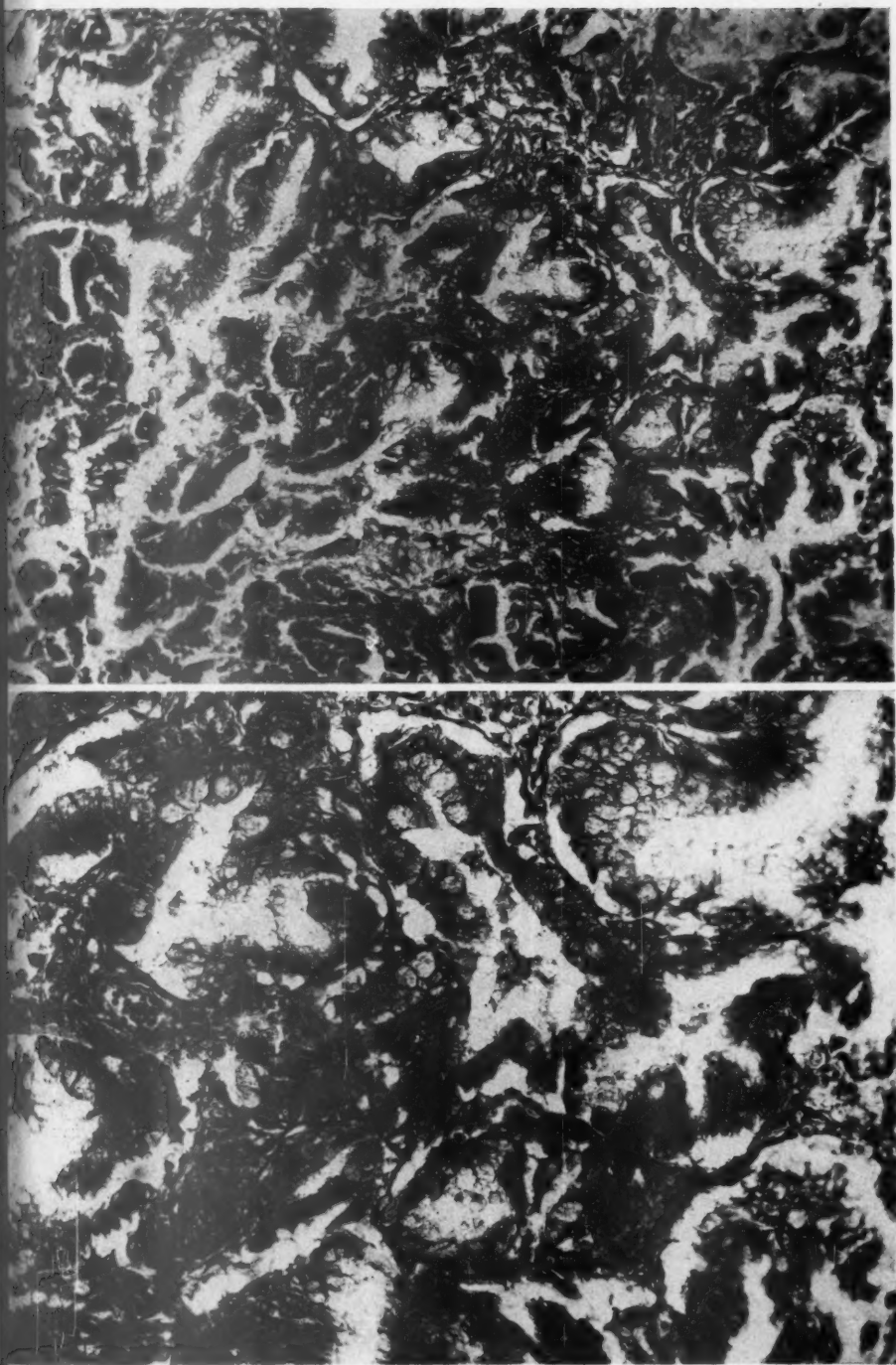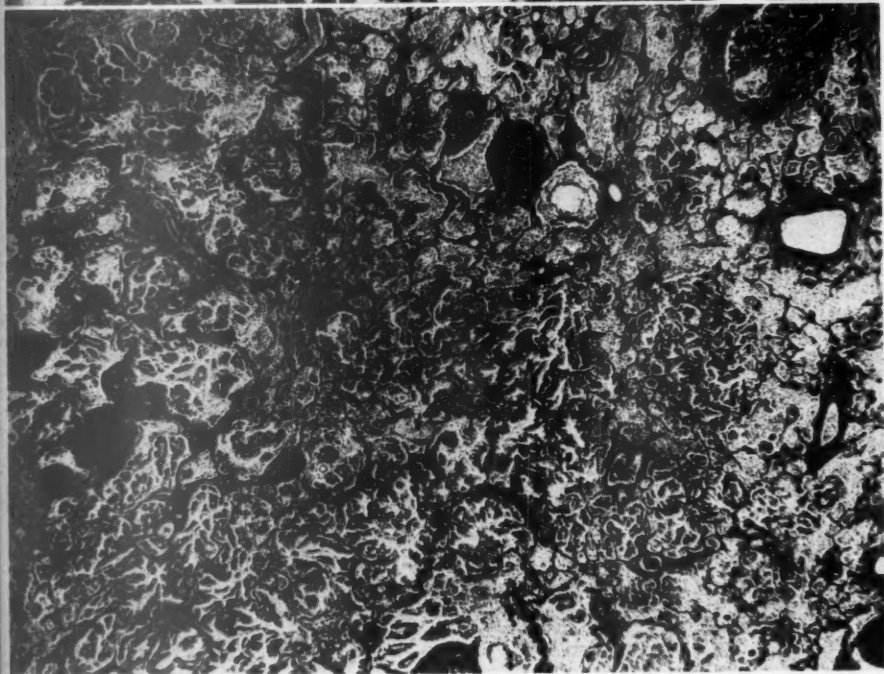
Simon   Pulmonary Adenomatosis

FIG. 5. Of note are the brush borders of cells lining the alveolus on the right and the character of the nuclei and cytoplasm. Hematoxylin and eosin stain. × 460.

FIG. 6. Low-power view showing the general distribution of pneumonia and of the neoplasm. Hematoxylin and eosin stain. × 23.

Simon

Pulmonary Adenomatosis

DISTINCTIVE CHARACTERISTICS OF THE SYMPATHICOBLASTOMA CULTIVATED IN VITRO

A Method for Prompt Diagnosis *

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The tumor here designated *sympathicoblastoma,* sometimes called *neuroblastoma,* is a highly malignant neoplasm composed of small sympathicoblasts which are often undifferentiated but sometimes arrange themselves in the form of rosettes or pseudorosettes. It is generally regarded as being derived from sympathetic nervous tissue, usually, although not always, arising in connection with a sympathetic ganglion in the mediastinal or retroperitoneal regions, or in the suprarenal medulla. Its chief incidence is among infants and young children, although it may be found in adults of various ages.

The observations here reported were gleaned in the course of a long-term study of the form and behavior of human tumors *in vitro,* during which eight sympathicoblastomas were investigated. These eight tumors behaved in a uniformly distinctive manner *in vitro;* their differences from other tumors with which they are likely to be confused clinically or histologically were so marked that we were led to use tissue culture as a diagnostic method for this tumor. By this means the diagnosis can now be made with a high degree of certainty in 24 hours or less.

Case Histories

Case 1

W. H. (S.P. 67384), an American boy, 3 years old, suffered for 3 months with symptoms due to metastases in the skull and elsewhere. When examined there were retroperitoneal masses and evidences of metastases throughout the skeleton, in the orbit, the scalp, and the abdominal wall. He died 6 weeks after admission to the hospital. Specimen taken for biopsy of one of the tumors in the scalp showed masses of undifferentiated sympathicoblasts with much hemorrhage and necrosis and no evidence of rosette or pseudorosette formation.

Case 2

Baby M (S.P. 73120), a male child of German-American parentage, was born with a large globular mass in the outer part of the left leg near the knee. After biopsy a mid-thigh amputation was done at the age of 1 month. Eighteen months later a retroperitoneal mass near the right kidney was explored and examined by biopsy. Roentgenotherapy was used over a period of 2 months but did not prevent the appearance of other metastases. When the child died at the age of 3⅓ years, autopsy showed metastases in the liver, right kidney, lungs, pleura, mesentery,

vertebrae, skull and humerus, from the retroperitoneal tumor. Microscopically, the tumor consisted of undifferentiated sympathicoblasts packed together tightly without the formation of either true or pseudorosettes.

Case 3

R. D. (S.P. 85876), an American male child, 12 months old, was found to have fluctuant swellings in both temporal regions and in the right thigh 1 week before admission. Tissue was taken for biopsy from the mass in the thigh and the child died 3 months later with extensive bone metastases and nodules in the abdominal cavity, pleurae, left lung, liver, and right testis. There was no autopsy but the primary site was believed to be retroperitoneal. Microscopically, the tumor was made up of sympathicoblasts which in some areas surrounded irregular spaces partly filled with tangled neurites. This represented partial differentiation. No perfectly rounded pseudorosettes were found.

Case 4

C. C. (S.P. 88130), a colored man, 33 years old, had noted a progressively increasing solitary swelling in the left groin. The mass was discrete, measured 8 by 5 cm., and was examined by biopsy. He received roentgenotherapy over a 1-month period. The field was 15 by 15 cm., later reduced to 10 by 10 cm. The factors were 190 kv., 10 ma., target skin distance 50, filter 1 mm. Cu, and a total dose of 3000 r. was given. As a result the tumor disappeared entirely and he was well 18 months after biopsy. Microscopically, the tumor was composed of solid masses of sympathicoblasts with extensive necrosis. Occasional pseudorosettes were present.

Case 5

H. F. (S.P. 88959), a boy, 6 years old, of Hungarian Jewish descent, complained of pain in the thoracic vertebrae for 6 months. Roentgenograms showed a mediastinal mass which at operation proved to be a lobulated, smooth, rubbery tumor, projecting into the right pleural cavity and pushing the trachea forward and the arch of the azygos vein downwards. It was impossible to remove the neoplasm completely and the child died 3½ months later. Microscopically, the tumor was made up of sympathicoblasts which formed a considerable number of pseudorosettes, and was extensively necrotic. It was found in a mediastinal node and involved a partly calcified sympathetic ganglion.

Case 6

R. A. (S.P. 90971), an American, 59 years old, developed nocturia and dysuria which persisted 6 months after prostatectomy elsewhere. It was reported that the prostate showed no tumor. At exploration a pelvic retroperitoneal mass was found. He died 3 days later, and at autopsy the tumor involved both seminal vesicles, the bladder wall, the prostatic bed, and had metastasized to the pelvic and retroperitoneal nodes. Microscopically, the biopsy section showed a tumor composed of solid masses and strands of rather well preserved, rounded, and sometimes slightly elongated hyperchromatic cells which showed no definite differentiation. The autopsy material showed the occasional formation of pseudorosettes and was very suggestive of sympathicoblastoma.

Case 7

D. F. (S.P. 93335), was an American male child, 16 months old. During a routine physical examination hard masses were felt in the umbilical region and the left flank. At exploration there was a retroperitoneal mass which extended from behind the cecum upward, pushing the stomach forward and the transverse colon downward. He was failing rapidly when he left the hospital 18 days later. Sections

taken for biopsy showed a tumor of sympathicoblasts, most of which were necrotic. In a few places pseudorosettes were present.

Case 8

A. A. (S.P. 97260), was an Italian-American female child, 13 months old. Following an attack of pneumonia, she was brought to the hospital with signs of fluid in the chest. When this was not confirmed an exploratory operation was performed and tissue was taken for biopsy from an inoperable mediastinal growth. She received some roentgenotherapy but the tumor did not regress and she was transferred to another hospital at the parents' request. Microscopically, the tumor was made up of sympathicoblasts which occasionally formed pseudorosettes and even immature ganglion cells. A Cajal impregnation showed many delicate neurites among the tumor cells. Occasionally one appeared to originate in a tumor cell.

MATERIAL AND METHODS

The material for explantation was obtained in the course of biopsy of either primary or metastatic sites. Both are equally satisfactory, so long as necrotic areas are avoided. Even the existence of inflammatory tissue associated with necrosis and hemorrhage does not vitiate the results if a fair number of viable tumor cells remain in the specimen used for explantation.

The tissue cultures were handled by the Maximow lying-drop method, modified slightly for our purposes (Murray and Stout, 1942). In the tumor the sympathicoblasts were grouped in solid masses with little supporting framework, thus forming a very friable tissue which broke up readily when cut or otherwise mechanically disturbed. Consequently, in setting out the cultures many fragments of various sizes were scattered through the medium. These small aggregates of pure tumor cells, uncomplicated by the presence of fibrous tissue, have been found to be more satisfactory objects for observation than the main explant.

Diagnosis can be made from the living cultures, but for records and for more detailed study permanent preparations are desirable. The reduced silver method of Bodian (1936), adapted to the cultures as whole mounts, is simple and reliable and furnishes brilliant contrast between neurites and background. For this it is best to fix the cultures in Bouin's fluid for ½ to 1 hour, and ripen in 80 per cent alcohol, with several changes, for at least 2 weeks before treating with silver. The following steps must be controlled with the microscope, but the approximate timing is as follows: protargol solution, 20 to 24 hours; hydroquinone, etc., 5 to 10 minutes; gold chloride, 1 minute; oxalic acid, 1 minute; sodium thiosulfate, ½ minute. Silver impregnation is the only histologic method in our experience which does justice to the finer structures of these sympathicoblasts (see Figures 3 to 5 and 7 to 11), but fairly satisfactory results can be obtained with phospho-

tungstic acid hematoxylin following Zenker fixation and omitting the Mallory bleach.

CHARACTERISTICS OF THE TUMOR IN VITRO

The sympathicoblasts do not migrate to any significant extent, but within 24 hours some of the small round or oval cells cohering in the clumps scattered about the clotted plasma have produced neurites of varying lengths, easily recognizable, and distinct from any form of outgrowth evolved *in vitro* by nonnervous tissues (Fig. 2). These neuroblasts, remaining *in situ*, project filamentous processes which are sometimes beaded, and which grow in the manner of an axone, with pseudopodial ends. The cells are usually monopolar, although sometimes bipolar and very occasionally multipolar. Within 48 hours the neurites have become longer and more numerous, and sometimes have begun to branch (Figs. 1 and 11). In favorable material this branching may become very elaborate as time goes on, so that after a fortnight's cultivation an isolated clump of cells may produce structures resembling a plexus (Figs. 8 and 10).

However, the sympathicoblasts as well as their newly grown neurites are very fragile, and overly responsive to handling; consequently it is best to confine the washing time to a maximum of 5 or 10 minutes, 2 or 3 times per week, and to keep the pH of the washing saline solution below 7.4. The viability of these cells *in vitro* is very variable and is probably connected with the original location of the explant within the tumor, whether it comes from a poorly nourished or moribund area or from a rapidly growing margin.

Necrosis among the cells composing the outer rim of a clump is so common as to be characteristic of this neoplasm *in vitro* (Figs. 4, 6, 8, and 11). This is not at all the case in clumps of cells derived from lymphosarcomas cultivated under the same conditions. Surprisingly, it reverses the pattern of necrosis which is commonly observed in sections of the sympathicoblastoma *in vivo*, in which the best preserved areas tend to lie close to the blood vessels and the pyknotic and necrotic regions are farther from the surfaces at which food, oxygen, and wastes may be exchanged. Such a pattern of necrosis as we observe *in vitro* leads to the inference that our tissue culture medium is not ideal for this material.

The cell body of the sympathicoblast is often about the size of a lymphocyte, though size may vary within a single tumor. The tumor cells may be larger, however, as in our case 7, in which they had two to three times the diameter of a lymphocyte. In this instance there was

considerable variation in size, and some rather large multipolar cells resembling more mature ganglion cells were present. Tumors have been reported (Stout, 1947) which combine ganglioneuromatous areas with others characteristic of the sympathicoblastoma, but we have not obtained one of these for cultivation. The sympathicoblastoma *in vitro* is entirely different from the benign ganglioneuroma, the behavior of which is essentially similar to that of nonneoplastic adult sympathetic ganglion cells (a description of which will be published shortly). These are large multipolar cells, which do not form tissues but remain isolated one from another and are relatively slow to grow and migrate.

Although the production of neurites is the most conspicuous trait of sympathicoblasts *in vitro*, these tumor cells are also prone to adopt epithelial formations. After 4 to 5 days *in vitro*, tongues or cords of cells appear, usually ending in a filamentous process (Figs 6 and 8). Cell boundaries in such an outgrowth are often indistinct, giving the whole mass the appearance of a syncytium. Nuclei are sometimes lobate or kidney-shaped, and since mitotic figures are only very rarely observed among them *in vitro* it is assumed that these nuclei may multiply by direct division. Within a week or more, flat membranes may be seen in favorable cultures; these differ from typical epithelial membranes in that they frequently develop dendritic outgrowths (Fig. 7). The sympathicoblastoma thus appears to be related to the neuro-epithelioma, one example of which we have been able to study in tissue culture (Stout and Murray, 1942). This exceedingly undifferentiated tumor, arising in the radial nerve, produced membranous sheets of epithelium when cultivated, but no neurites. The neuro-epithelioma might possibly be compared to the neural plate stage in nervous development. It seems probable that the sympathicoblastoma typifies a state of differentiation similar to that found in the neural tube stage of the embryo, since the tumor cells are small, capable of forming membranes *in vitro* (as does columnar epithelium from other germ layers), and are unaccompanied by satellite cells of any description. The rosette formations found in sections of neuroblastomas in general have been thought to represent cross sections of neural tubes formed in these neoplasms.

By the fourth day *in vitro*, fibroblasts are fairly numerous. At the end of 1 week, neurites and other evidences of the sympathicoblasts in the explant are usually obscured by the fibroblastic growth, but the islands of pure neuroblasts scattered throughout the clot may remain distinct for at least 1 month (Fig. 5), the duration of our observations.

Explants of these tumors frequently contain considerable numbers

of lymphocytes and other blood elements, which migrate out into the clot. Differences in form are usually sufficient to distinguish these from the neoplastic cells, but the distinction may be heightened by vital staining with basic dyes. The living sympathicoblasts stain quickly with neutral red applied supravitally in a dilution of 1:10,000. The stain may appear in the cell as a compact group of small granules occupying a juxtanuclear position, or as a few scattered granules in a diffusely pink cytoplasm. In either case the sympathicoblast can be distinguished readily from the normal or neoplastic lymphocyte, which, although it may aggregate in clumps, does not take up neutral red at all. The addition of a dilute solution of Janus green B to the neutral red solution serves to emphasize the distinction further, since the sympathicoblasts contain few or no Janus green staining particles, while the lymphocytes take up the dye readily.

DISCUSSION AND SUMMARY

The cultivation of the sympathicoblastoma *in vitro* provides a more rapid as well as a more certain means of identifying this tumor than the customary histologic section methods. Frozen sections are often unsatisfactory; they are particularly unreliable in distinguishing the sympathicoblastoma from members of the lymphosarcoma group or from the small-celled carcinomas.

Small fragments of the tumor, isolated in the medium of clotted plasma, can be counted on to produce neurites within 24 hours. This faculty, coupled with the tendency to marginal necrosis and the affinity of the tumor cells for neutral red applied supravitally, provides a very satisfactory means of differential diagnosis between this tumor of nervous origin and the lymphosarcomas and Ewing's tumor with which it is sometimes confused clinically. As cultivation is continued, from 2 to 5 days, the whole picture becomes increasingly clear and distinctive. There is great advantage in being able to see the whole cell with all its processes and extensions, as well as the characteristic patterns in which the cells group themselves. When this can be done, the sympathicoblasts present a very different appearance from lymphocytes. or lymphoblasts or from small carcinoma cells.

Of the eight tumors which we have studied *in vitro*, two have occurred in adults, aged 33 (case 4) and 59 (case 6) years, respectively. Because of their equivocal histologic features these could not be accepted as unquestionable sympathicoblastomas without the examination *in vitro*.

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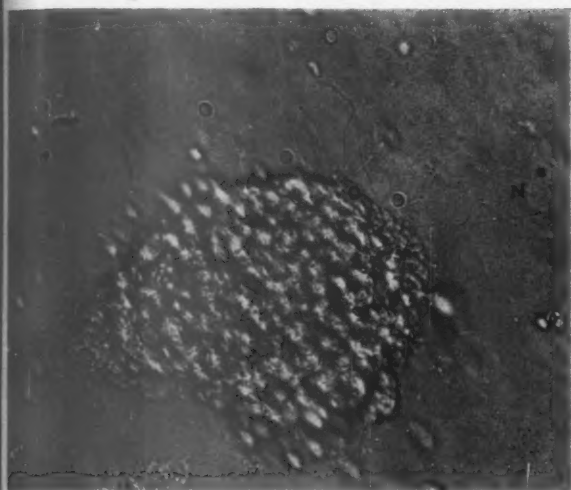
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 72

FIG. 1. Case 8. Living isolated clump of sympathicoblasts, with neurites (N) having pseudopodial ends; 48 hours *in vitro*. × 290.

FIG. 2. Case 8. Living clump of sympathicoblasts with neurites (N); 24 hours *in vitro*. × 290.

FIG. 3. Case 4. Small clump of sympathicoblasts (S) with neurites (N); F indicates a fibroblast; 10 days *in vitro*. Bodian method. × 380.

FIG. 4. Case 4. Clump of sympathicoblasts (S) with branching neurite (N), and marginal necrotic area (Ne). Flattened fibroblasts (F) are shown for comparison of size; 10 days *in vitro*. Bodian method. × 380.

FIG. 5. Case 5. Isolated clump of sympathicoblasts (S) with neurites (N) surviving 30 days. F is a fibroblast. Bodian method. × 255.
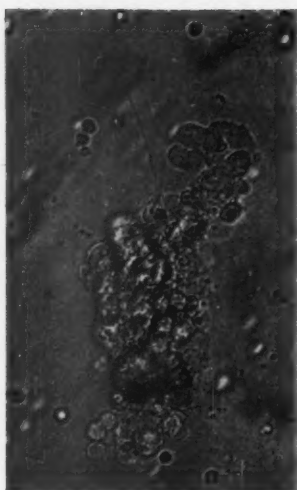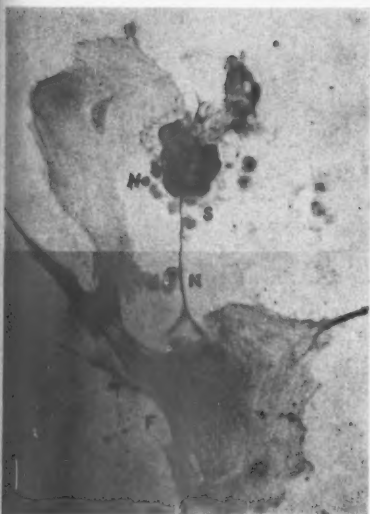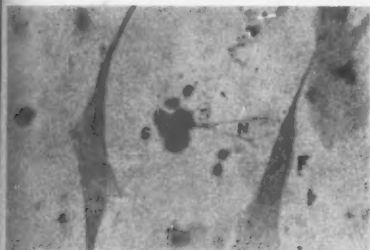
Murray and Stout

Sympathicoblastoma Cultivated *in Vitro*

FIG. 6. Case 3. Isolated clump with projecting tongues of neuro-epithelium (N-E) ending in neurites (N), and marginal necrosis (Ne); 5 days *in vitro*. Phospho-tungstic acid-hematoxylin stain. ✕ 305.

FIG. 7. Case 3. Sympathicoblasts growing as a flat epithelium (N-E) with neurites (N). Fibroblasts (F). 17 days *in vitro*. Bodian method. ✕ 245.

FIG. 8. Case 3. Clump of sympathicoblasts with pyknotic center, necrotic margin (Ne), epithelial tongues (N-E), and many branched and beaded neurites (N); 5 days *in vitro*. Bodian method. ✕ 220.
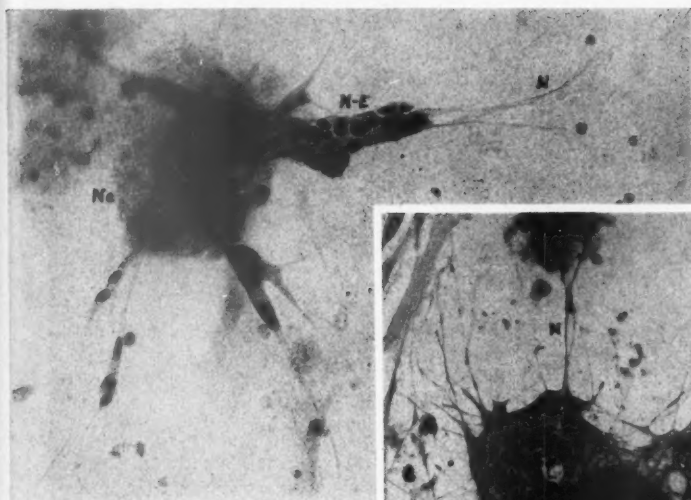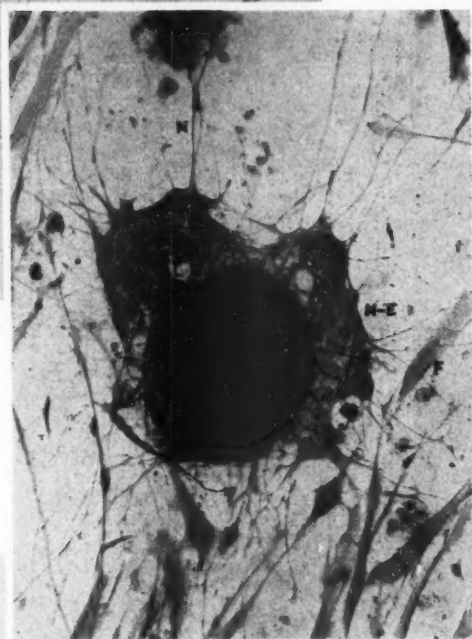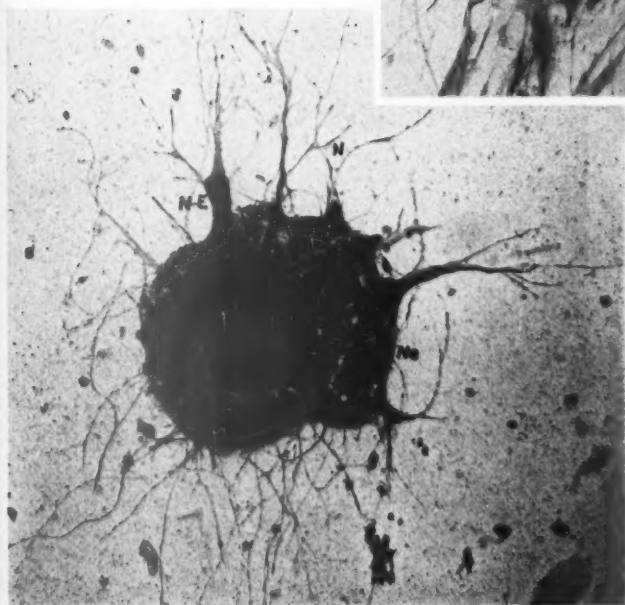
PLATE 74

FIG. 9. Case 5. Membranous clump of sympathicoblasts (S) with very long, beaded neurites (N); 7 days *in vitro*. Bodian method. × 245.

FIG. 10. Case 3. Neurites (N) tending toward plexus formation; necrotic material (N-E); young fibroblasts (F); 17 days *in vitro*. Bodian method. × 140.

FIG. 11. Case 6. Clumps of sympathicoblasts (S), with necrotic margins (Ne) and neurites (N) at 48 hours. Bodian method. × 360.

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Sympathicoblastoma Cultivated *in Vitro*

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INTESTINAL LIPODYSTROPHY OF WHIPPLE
REPORT OF A CASE AND ANALYSIS OF THE LITERATURE *

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In 1907 Whipple [1] described a disease which he believed to be unique in the literature and for which he proposed the name intestinal lipodystrophy. It was characterized clinically by steatorrhea, progressive weakness, and weight loss; and pathologically by dilatation of the lacteals in the small intestine, of the mesenteric lymphatics, and of the sinuses of the mesenteric lymph nodes, with accumulation of intracellular and extracellular fatty materials at these sites.

Apparently no similar case was reported until 1923, when Blumgart [2] described 3 fatal instances of what he called malabsorption of fat, which he felt resembled Whipple's case in many respects. Unfortunately, Blumgart's cases are difficult to evaluate, due to apparent inconsistencies between his abstracts of the autopsy protocols and his summary of them. Later authors have sometimes accepted all 3 of Blumgart's cases and sometimes only his second. Reports of unexplained diarrhea or steatorrhea with pathologic findings reminiscent of Whipple's original description have become increasingly prominent during the past 10 years. Because it is not yet clear whether Whipple's disease is a distinct entity, and if it is, exactly what features constitute the entity, there has been much confusion as to which cases should be included under the designation intestinal lipodystrophy. Some cases have been called Whipple's disease by some authors and discarded or overlooked by others. At least one or two other cases, not included in recent reviews, probably belong in the group. Possibly there are many others, lost in the literature under various designations, which could be included.

In 1936 Jarcho [3] presented what he believed to be the third case of Whipple's disease, since he accepted only Blumgart's [2] second case. The following year Hill [4] described a case of "mesenteric chyladenectasis," which was in many respects similar to Whipple's original description, but which Hill himself did not identify with this group. Reinhart and Wilson,[5] in 1939, reported a case of intestinal lipodystrophy and reviewed the descriptions of Whipple,[1] Blumgart,[2] Jarcho,[3] and Boeck.[6] Boeck's case had been presented briefly in 1938, in a discussion of pancreatic insufficiency, as an instance of steatorrhea.

The next review of the disease as such was by Sailer and McGann,[7]

in 1942. These authors, while reporting an additional case, reviewed the literature and included in the group the cases of Whipple, Blumgart (all 3), Jarcho, Hill, Boeck, and Reinhart and Wilson. In addition, they added those of Fleischmann [8] (1930), and Korsch [9] (1938), previously overlooked. Thus, with their own case, they brought the number up to 11. In the same year (1942) Pearse [10] presented a case diagnosed during life, the patient still being alive at the time of publication. Whipple himself had reviewed the slides of the biopsy material and believed the cellular picture to be similar to that in his own case. However, the intestine and mesenteric lymph nodes were not examined. If Pearse's description is to be considered consistent with Whipple's disease, then the second case of Collins and Berdez [11] certainly should be included.

From this period the literature became more and more inconsistent. Apperly and Copley,[12] in 1943, reported what they considered to be the 12th case. Actually, if all the above-mentioned cases were included, it would be the 14th since these authors made no mention of the cases of Pearse[10] or of Collins and Berdez.[11] In their report they included a tabulation of the symptoms and pathologic findings in the 12 cases.

In November, 1945, 2 case reports of Whipple's disease appeared in different journals. One was that of Amsterdam and Grayzel,[13] who reproduced the tabulation of Apperly and Copley,[12] and added to it their own case and that of Vaux [14] (1943). However, it is probable that they should have included also a case to which Vaux had referred, that of Glynn and Rosenheim [15] (1938), which Vaux considered to be in a class with her own case and that of Hill.[4] The other case was that of Fitzgerald and Kinney,[16] who considered theirs to be the 8th instance of Whipple's disease. Actually, if all the others are included, except that of Amsterdam and Grayzel which appeared simultaneously with it, this must be considered the 17th case. Fitzgerald and Kinney included in the group the following cases: Whipple, Blumgart (second case only), Jarcho, Reinhart and Wilson, Sailer and McGann, Korsch, Pearse, and their own. They excluded Blumgart's first and third cases, and those of Fleischmann, Boeck, and Hill. They apparently were not aware of the reports of Apperly and Copley, Vaux, Glynn and Rosenheim, and Collins and Berdez.

Finally, attention should be called to Thannhauser's [17] discussion of Whipple's disease. Thannhauser believed that the descriptions of Whipple [1] and of Reinhart and Wilson [5] coincided with those in cases of "xanthomatous transformation" of the mesentery, in which accumulations of foamy cells in the mesenteric fat are incidental findings at autopsy and are probably secondary to inflammation of the fat or to fat

necrosis from various causes. We shall describe such foci in our own case. Unfortunately, we have not been able to find any mention of such lesions in either Whipple's or Reinhart's descriptions; and the photomicrograph from Reinhart's case which Thannhauser reproduced was apparently obtained through a personal communication. Thannhauser believed that the cases of Jarcho [3] and Blumgart [2] do not belong here, as those authors did not describe such xanthomatous transformation. Needless to say, these comparatively insignificant xanthomatous deposits in the mesentery might easily have been overlooked by Jarcho and Blumgart, as in the other cases, in view of the more striking pathologic findings. Certainly it would seem that the cases referred to by Thannhauser have little in common with our own case or the other reported cases of intestinal lipodystrophy; and that in our own case, at least, the mesenteric accumulations of foam cells were secondary to the intestinal and lymphnodal deposits, perhaps from a spilling over of fats from ruptured lymphatics, rather than representing the primary lesion.

It is our opinion that the typical lesions of Whipple's disease as described by him were the massive accumulations of intracellular and extracellular fat in the small intestine and its draining lymph nodes, with dilatation (probably resultant) of lacteals and mesenteric lymphatics; and that if these are considered the pathologic criteria for the disease, the only cases that definitely can be included after Whipple's case, at least until more is known about the pathogenesis, are, in chronologic order, those of Jarcho, Hill, Korsch, Glynn and Rosenheim, Reinhart and Wilson, Sailer and McGann, Apperly and Copley, Vaux, Amsterdam and Grayzel, and Fitzgerald and Kinney. We would exclude those of Blumgart because of the incompleteness and inconsistencies of his descriptions; of Pearse, because neither the intestine nor mesenteric lymph nodes were examined; and of Fleischmann, because the intestine apparently was not involved. Boeck's case is doubtful, because the involvement of mesenteric nodes, found at laparotomy, was no longer present at autopsy 4 months later, although fat deposits were noted in the wall of the small intestine. The case of Collins and Berdez is also doubtful because of inadequate description of the intestinal lesions. It is possible that when more is known of the pathogenesis of this disease, at least some of the cases which we have excluded may be considered early or less advanced instances of the disease.

The following case satisfies the criteria we have suggested above, and we therefore consider it to be the 12th such case. If all the cases reviewed above should be included, however, our case brings the total, so far as we have been able to ascertain, to 19.

REPORT OF CASE

The patient, I. W. (autopsy no. 10205), was a Russian-born white female, 54 years old, who was seen on April 10, 1945, by a private physician. She complained of increasing abdominal pain, weight loss of 10 lbs. in 6 months, poor appetite, and obstinate constipation.

On April 22, 1945, the patient entered Bronx Hospital. Her complaints then were weight loss of 15 lbs., weakness, and diarrhea of 2 weeks' duration. She stated that she had 4 to 5 bowel movements daily and that the stool was dark green and showed no blood. Prior to the onset of diarrhea, she had been constipated for several years, taking senna without effect.

On examination, the patient was lying in bed, in no apparent distress. Malar telangiectases were noted. The blood pressure was 112/60 mm. Hg. Heart and lungs were negative. The abdomen was large and distended. A mass, later interpreted as spleen, was felt 4 fingersbreadth below the costal margin in the left side. There was no peripheral edema. Reflexes were normal.

Laboratory Findings. The urine showed a trace of albumin. Examinations of the blood on two occasions revealed the hemoglobin to be 72 and 68 per cent; red blood cells, 4.61 and 4.27 million; white blood cells, 14,500 with 37 per cent polymorphonuclear leukocytes, 54 per cent lymphocytes, 8 per cent monocytes; and white blood cells, 11,700 with 43 per cent polymorphonuclear leukocytes, 54 per cent lymphocytes, 1 Türk cell. Icterus index was 7. Total cholesterol was 142.9 mg. with 57 per cent esters. Stool culture was negative for the typhoid-dysentery group, and there was no occult blood. Sternal puncture revealed normal bone marrow. Total proteins were 6.33 gm., with 3.32 gm. of albumin, and 3.01 gm. of globulin. Takata-Ara test was negative. Cephalin flocculation test was 2 plus. The Wassermann test was doubtful and the Kahn test negative on one occasion, but later each was reported as 4 plus. Roentgenograms of the abdomen showed the spleen to be enlarged to the umbilicus, and a stone of biliary type in the gallbladder region.

The patient was afebrile throughout her stay. On April 26 a moderate amount of fluid was noted in the abdomen. She was discharged on May 15, 1945, with the final diagnosis of cirrhosis of the liver and lues.

She entered Montefiore Hospital on May 29, 1945. She then complained of having had "heart disease" for 3 months, diarrhea and weight loss for 2 months. There had been no vomiting and no tarry or bloody stools. She claimed to be having eight bowel movements a day. There was also a dubious history of numerous bouts of congestive circulatory insufficiency.

Examination revealed a "noisy" female with no dyspnea or orthopnea. Temperature was 98°F.; pulse, 90; blood pressure, 108/62 mm. Hg. Pupils were contracted and reacted poorly to light. There was an apical systolic murmur and an accentuated second aortic sound. The abdomen was distended. The spleen was felt 4 fingersbreadth below the costal margin. There was 1 plus pretibial edema. Reflexes were hypoactive. The impressions were: Banti's syndrome; general paresis; acute gastro-enteritis.

Laboratory Findings. The Wassermann and Kahn tests were 4 plus; Kline test, 3 plus. Urine: specific gravity, 1.020 and 1.013, with albumin 0 to a trace; glucose, a trace to 2 plus; up to 10 white blood cells per high power field. No blood count was done.

The patient received antiluetic therapy in the form of bismuth in oil, liver injections, and mercupurin. The diarrhea subsided somewhat. On July 3, 1945, abdominal paracentesis released 2500 cc. of straw-colored fluid with 0.8 per cent protein. During the last few weeks of her life increasing "muddy" pigmentation of the skin was noted. She had periods of confusion, hysteria, and depression. Her mental status was considered to be due to tertiary lues.

On July 17, 1945, the patient suddenly had copious coffee-ground vomitus, went into shock, and appeared to aspirate much vomitus, soon becoming livid. All measures to relieve her were futile and she died about 4 hours after the onset of these symptoms.

AUTOPSY FINDINGS

Autopsy was performed 2 hours post-mortem by Dr. Ruth Lubliner and was reviewed by us. The body was that of a fairly well developed and nourished middle-aged white female, 57 inches in length. There was cyanosis of face, lips, ears, and neck. Numerous scratches were noted on the breasts, abdomen, and arms, and petechial and larger hemorrhages were present over the chest. There were brownish crusts in the nostrils and on the lips. Moderate dependent edema was present. Peripheral lymph nodes were not enlarged. The abdomen was distended and the abdominal cavity contained about 2000 cc. of opalescent, milky, somewhat yellowish fluid, in which a large amount of soft, opaque, whitish, curd-like material was suspended. The serosal surface of the small intestine and the pelvic peritoneum were covered with shreds and sheets of similar material. There were a few easily torn fibrous adhesions. A fairly large amount of fat was present in the usual depots. The liver extended about 6 cm. below the costal margin. The spleen was enlarged, displaced anteriorly, and extended along the costal margin from the mid-axillary line to the mid-clavicular line. There was marked engorgement of all superficial and deep veins. The pleural cavities were free of fluid. Some fibrous adhesions were present over the right lung.

There were submucosal hemorrhages in the larynx, trachea, and pharynx; and subpleural punctate hemorrhages over the lower lobe of the right lung. The lungs showed marked edema. The bronchi contained no blood or aspirated material. There was considerable variation in the appearance of the hilar and tracheobronchial lymph nodes. Many, as commonly seen in this location, were small, fairly firm, and deeply anthracotic. However, several of the bronchial nodes, on the left side only, and especially those just below the bifurcation of the trachea, were enlarged to about 1.5 or 2 cm. Some of these were fluctuant and opaque grayish white to yellowish. On section they were found to be largely reduced to a shell enclosing a thick opaque fluid material with a somewhat greenish tint probably due to admixture with anthracotic pigment. Others were moderately firm, partly deeply anthracotic, and partly grayish white with numerous soft, opaque whitish or yellowish white foci of 1 mm. or less and very little anthracotic pigment. The heart weighed 240 gm. and was flabby. The aorta and coronary arteries showed moderate arteriosclerosis. The liver

weighed 1800 gm.; section revealed swollen reddish to yellowish brown lobules. The gallbladder contained 40 cc. of viscid bile and several irregular, friable, dark green calculi. The spleen weighed 380 gm. and was flabby. The capsule was irregularly thickened. The cut surface was mottled reddish gray with small, dark red foci, and did not scrape. The pancreas appeared normal. The right adrenal weighed 7.5 gm. and the left, 8 gm. The cortex was broad and yellowish brown. The kidneys each weighed 150 gm. and were flabby. The capsule stripped easily from a smooth surface. Bone marrow of the lumbar vertebrae was pale red-brown. The thyroid gland weighed 12 gm.; translucency was slightly decreased. Examination of the brain and cord was not permitted.

The outstanding changes were in the gastrointestinal tract and abdominal lymph nodes. The lower third of the esophagus showed a granular hemorrhagic mucosa. There was marked spasm of cardia and pylorus. The stomach was contracted and contained a small amount of brownish mucus.

The small intestine was distended with a large amount of pale yellowish, very soft, unformed material. The wall was thickened and rather rigid, the lumen dilated up to 1½ times the normal circumference. The valvulae conniventes measured up to 2 to 3 mm. in thickness and up to 6 mm. in height, and between them the wall measured up to 1.5 cm. in thickness. The entire mucosal surface had an opaque, whitish or yellowish white, rather milky appearance, which on the whole was diffuse, but which here and there left patches of normal color with scattered opaque, yellowish white spots (Fig. 1-b). On closer inspection the coloration was seen to be due to myriads of opaque, yellowish white, slightly elevated foci, pinpoint to pinhead in diameter, and up to 0.5 mm. or more in height, closely spaced and giving the surface a granular or plush-like appearance. These foci, apparently enlarged villi, became confluent in large areas, especially over the circular folds. Cross section of the intestinal wall revealed occasional opaque, whitish or yellowish white spots, probably dilated lymphatics, in submucosa, muscularis, and serosa (Fig. 1-a). Similar spots and streaks could be seen on the serosal surface. Occasionally there were soft nodular elevations of this color up to about 1 cm. in diameter and 4 or 5 mm. in height. On incision milky fluid was released from these, leaving a smooth-lined space, presumably a dilated lymphatic. Similar milky fluid seemed to exude from the entire cut surface of the intestine. These foci in the serosa seemed to be most numerous along the mesenteric attachment, where they could frequently be seen continuing into the mesenteric fat. The changes described above began abruptly

immediately beyond the pyloric ring and ended with the same abrupt-
ness at the ileocecal valve; they were somewhat more pronounced in
the duodenum and jejunum than in the ileum. The Peyer's patches and
solitary lymph follicles were not unusual. The appendix was normal.
The entire colon was filled with fecal material similar to that in the
small intestine. There were no formed contents.

Striking changes were seen in all abdominal lymph nodes. They
ranged from 0.5 to 2 cm. in greatest dimension, the larger being mesen-
teric and periesophageal. The nodes were discrete, soft, and some-
times fluctuant. On section the smaller ones consisted partly or en-
tirely of soft, friable, opaque, whitish, cheesy material. The larger
nodes were reduced in part or completely to cyst-like structures con-
taining a milky fluid or opaque, yellowish, creamy material.

There was marked thickening of the mesentery, which, in addition
to the altered lymph nodes, contained numerous opaque, whitish or
yellowish white pinhead and larger spots and streaks, seen through the
peritoneum and on the cut surface (Fig. 1-a). On section these re-
leased a milky fluid; they were interpreted as dilated lymphatics.
There were also many irregular, opaque, pale yellowish areas from
pinhead to a few cm. in size in the mesenteric fat (xanthomatous foci).
The omentum showed similar changes. In its upper portion there was
a large cyst-like space about the size of a plum. It was lined by a
thick layer of soft, friable, whitish, curd-like material, and was inter-
preted as an encapsulated chylous effusion.

Microscopic Examination

Examination of the tissues other than small intestine, lymph nodes,
and mesentery confirmed the gross findings.

Small Intestine. There was marked enlargement of most of the
villi of the small intestine, both in length and in breadth, producing
bizarre club-shaped, pear-shaped, or globoid forms (Fig. 2). Expan-
sion was due mainly to the accumulation of large amounts of deep pink
coagulum which appeared to lie mainly in the stroma and was thinly
scattered with lymphocytes and a few macrophages. In places this
material still occupied large spaces, lined by endothelial cells, pre-
sumably dilated lacteals. There was an excess of lymphocytes, plasma
cells, and eosinophils throughout the propria, and some proliferation
of fibroblasts and young capillaries. The submucosa contained a few
dilated lymphatics filled with a paler pink coagulum, sometimes with a
few large foam cells; or occasionally distended with a mass of foam
cells. Between these the submucosa appeared edematous and con-
tained a thin scattering of lymphocytes, plasma cells, and macrophages,

as well as masses of foam cells. In only one or two places a large
space, apparently representing dissolved-out lipoid, was surrounded by
elongated multinucleated cells which had curved around it, and beyond
these a zone of lymphocytes and macrophages. Greatly dilated lymph-
atics lay in the subserosa; these contained pale granular, highly vacuo-
lated or foamy pink-staining material. In places in the subserosa there
was also considerable deeper pink coagulum, containing a few foam
cells, lying free. Here and there a few small masses of fibrin were pres-
ent in the serosa. The latter was considerably thickened by proliferat-
ing fibroblasts and capillaries and by considerable diffuse and more
marked focal infiltration of lymphocytes, a few plasma cells, and
numerous macrophages. The macrophages were often greatly swollen
and foamy and were more diffusely scattered than the other infiltrating
cells. The foamy cells also appeared in well defined clumps in the sub-
serous fat.

Lymph Nodes. Sections of several of the abdominal nodes, includ-
ing mesenteric, periesophageal, and peripancreatic, and of a left
tracheobronchial node showed striking changes (Figs. 4 and 5). The
lymph sinuses, both cortical and medullary, were widely dilated and
distended with deep pink-staining material, sometimes homogeneous,
sometimes finely or more coarsely vacuolated, and so dense that often
it had fragmented under the knife like colloid. The intervening lymph-
atic cords were markedly compressed and reduced to rather narrow
strands densely packed with lymphocytes, and in places infiltrated with
plasma cells and occasional eosinophils. Mingled with the coagulum
were large numbers of tremendously swollen foamy macrophages, to-
gether with a sprinkling of lymphocytes, plasma cells, and, in places,
numerous polymorphonuclear leukocytes. Where there was less coagu-
lum, the lipophages lay in closely packed masses and sheets. Scattered
foam cells also were present throughout the lymphatic cords. In some
of the nodes there were a few small hemorrhages into the sinuses and
small accumulations of free and phagocytosed blood pigment. In a
periaortic node, the pink-staining coagulum was not found, but there
was a scattering of foamy cells through it. In this node there also were
proliferation and desquamation of reticulo-endothelial cells into dilated
sinuses, and many plasma cells, polymorphonuclear leukocytes, and
especially eosinophils in the sinuses and infiltrating the lymph cords.

Mesentery. In addition to the changes in the lymph nodes already
described, the mesenteric lymph vessels were widely dilated and filled
with the same material as the nodal sinuses (Fig. 3). Blood vessels
were engorged. The fat showed slight diffuse and more marked focal
infiltration of lymphocytes and plasma cells. Scattered throughout the

fat were small and large accumulations of foam cells, reaching xantho-
matous proportions. These foam cells, like those encountered previ-
ously, varied from slightly larger than the usual macrophages to per-
haps 30 or 35 μ. They had a sharply defined, sometimes thick, deep
pink cell membrane and a tremendously ballooned-out, frothy, fairly
uniformly vacuolated, pale pink cytoplasm. The nucleus was usually
eccentric, small, dark, round, and often pyknotic.

Special stains were done on sections of a mesenteric lymph node
and small intestine. With sudan IV the coagulum in the lymph vessels,
lacteals and in the interstitial tissue of the bulbous villi as well as the
cytoplasm in the foam cells took a brilliant reddish orange hue, varying

TABLE I

Results of Chemical Analysis

	Mg. per 100 mg. of dried tissue	
	Mesenteric lymph nodes	Jejunum
Total lipids	73.5	53.4
Phosphatids (26 × lipid P)	5.8	4.9
Cholesterol	6.1	4.2
Total fatty acids	64.0	41.5
Free fatty acids	12.1	5.7
Saponification number	166	150

somewhat in intensity. With Nile blue sulfate there was considerable
variation from the bright pink of the neutral fat, seen in the normal
mesenteric fat and probably the predominant hue in the fatty deposits,
through pinkish lavender and bluish lavender to deep royal blue.

Chemical analysis of an alcohol-ether extract of formalin-fixed
mesenteric lymph nodes and a section of jejunum was done by Dr.
Emil J. Baumann. Several heavily involved mesenteric lymph nodes
and a few small segments of jejunum were freed as completely as pos-
sible of their external adipose tissue and pooled for the chemical analy-
sis. This analysis showed a high lipid content, consisting predomi-
nantly of neutral fats, with lesser amounts of phospholipids, choles-
terol, and free fatty acids. The saponification number was lower than
that for normal tissue (Table I).

Anatomic Diagnoses. Latent lues (clinical); intestinal lipodystrophy
(Whipple's disease) involving small intestine, mesentery, and omen-
tum, and mesenteric, peripancreatic, periportal, perigastric, peri-
esophageal, periaortic, and left tracheobronchial lymph nodes; chylous
ascites; distention of small intestine with fecal material; petechial and
larger hemorrhages in skin, larynx, trachea, pharynx, esophagus,
pleura, and vaginal mucosa; engorgement of all peripheral and deep

veins; edema of lower extremities and dependent part of abdomen;
marked cyanosis; chronic splenitis with splenomegaly; peritoneal ad-
hesions; subacute esophagitis; edema of lungs; severe parenchymatous
degeneration of heart, liver, and kidneys; generalized arteriosclerosis;
melanosis coli; multiple lipomas of cecum and ascending colon; chole-
lithiasis; large adenoma of right kidney; patchy fibrosis of upper lobe
of right lung; pleural adhesions; small cholangioma of liver; small
intramural uterine fibromyomas; small fibromyoma of stomach.

COMMENT

As in the previously reported cases of Whipple's disease, our patient
was of middle age, and had gastrointestinal symptoms of relatively
short duration, complaining of abdominal discomfort, asthenia and
weight loss, and diarrhea. As in many or all of the other cases, there
were pigmentation of the skin, peripheral edema, moderate anemia, low
blood pressure, and absence of fever. Pathologically, the outstanding
findings were limited to the small intestine, regional and some distant
lymph nodes, and the mesentery, and were unlike those described for
any other known disease.

Unlike any of the other reported cases, except Blumgart's [2] second,
and that of Collins and Berdez,[11] both of which we consider to be ques-
tionable examples of this disease, our patient was a female. There was
no history of arthritis, such as has been described in several cases, and
clinically, at least, no definite steatorrhea. In addition, our case pre-
sented a few interesting features, noted in at least some previous
reports, which may or may not be a part of the syndrome. For one
thing, the sudden death, clinically considered asphyxial in nature,
could not be explained adequately at autopsy. Several other patients
died suddenly, without satisfactory explanation. Whipple's [1] patient
died in respiratory distress 2 days following surgical exploration of the
abdomen. In Reinhart and Wilson's [5] case, the patient suddenly be-
came cyanotic and died. Fitzgerald and Kinney's [16] patient died sud-
denly at home 24 hours after leaving the hospital. Sailer and Mc-
Gann's [7] patient also died suddenly following an attack of acute ab-
dominal pain. Blumgart's [2] first patient and Boeck's [6] patient both died
apparently in acute cardiac decompensation. In none of these cases
was death satisfactorily accounted for on the basis of the anatomic
findings.

Moderate hepatosplenomegaly was noted in several of the reports.
In Reinhart and Wilson's [5] case it must be discounted, since there was
portal cirrhosis. In Fitzgerald and Kinney's [16] case the clinical picture
and the findings in the surgically removed spleen were consistent with

a diagnosis of hemolytic jaundice. Whipple [1] gave the weights of liver and spleen as 2570 and 375 gm., respectively, the latter showing "chronic splenitis." Korsch [9] merely noted that the liver and spleen were enlarged. In Apperly and Copley's [12] case the liver weighed 2200, the spleen, 320 gm.; microscopically, the former presented peculiar granulomatous nodules; the latter, some nonspecific changes. In our own case the liver was perhaps slightly enlarged (1800 gm.), the spleen moderately (380 gm.), apparently due to a combination of congestion and splenitis.

Leukocytosis with relative and absolute lymphocytosis was described by Reinhart and Wilson,[5] in whose case it led to a clinical diagnosis of benign pseudoleukemic lymphocytosis; by Fitzgerald and Kinney,[16] whose case was followed for some time as lymphatic leukemia and the patient treated with radioactive phosphorus; and was present in our own patient, in whom the diagnosis of lymphatic leukemia was also entertained for a period, especially in view of the accompanying splenomegaly. Fitzgerald and Kinney were unable to give any explanation for the lymphocytosis other than that it was an "unusual type of lymphocytic or histiocytic response of unknown causation." It is our belief, however, that the lymphocytosis may be related to the lymph stasis in the small intestine. Bunting and Huston [18] showed that the number of lymphocytes entering the blood stream daily from the thoracic duct is greater than the total number demonstrable in the blood at any one time, and postulated that lymphocytes in large numbers are excreted from the blood stream into the lumen of the alimentary tract. According to Thompson,[19] streams of lymphocytes flow from the lymphoid tissue of the alimentary canal in two directions: towards the lumen of the bowel and towards the subserous lymphatics. In the intestine, the migration of lymphocytes is predominantly into the lumen of the gut.

On the other hand, Erf [20] demonstrated in rabbits that the rôle of the gastrointestinal tract in the excretion of lymphocytes is readily taken over by other forces within the body. We, ourselves, have seen a leukocytosis of 160,000 (100 per cent polymorphonuclear) develop after abdominoperineal resection in a patient with chronic ulcerative colitis, drop to 40,000 in 1 day, and return to normal levels within 2 weeks, accompanied throughout by a normal bone marrow. The interpretation * was that the diseased colon had called forth a marked local increase in polymorphonuclear leukocytes; and that with its sudden removal these cells, still being produced in excess by the marrow and no longer being excreted at the usual site, had piled up in the peripheral blood. Un-

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doubtedly the balance between production and destruction of leuko-
cytes is a delicate one; and when a portion of the mechanism is put out
of commission, the ability of the rest of the system to take over either
or both functions will vary with the individual. It is conceivable that
the accumulation of fat in the intestinal mucosa in Whipple's disease
can impede the usual excretion of lymphocytes through this mucosa;
and that in the 3 instances of lymphocytosis enumerated above, the
other excretory sites had not completely substituted for the bowel.
Also to be taken into consideration is the rôle that leukocytes play in
the transport of fats,[21] with the possibility that the massive deposits
of fat in the intestine may be a stimulus to mobilization of lymphocytes.

Morphologically, our case demonstrated another feature of interest
in the extent of involvement of the lymph nodes. In most of the previ-
ous reports, only the mesenteric nodes, sometimes with the peripan-
creatic, showed the characteristic changes. In a few, the retroperitoneal
nodes were also involved. Fitzgerald and Kinney [16] found also slight
involvement of paratracheal nodes, and Reinhart and Wilson,[5] and
Apperly and Copley,[12] of mediastinal nodes. Korsch [9] described, in
addition to mesenteric and retroperitoneal nodes, enlarged mediastinal,
paratracheal, and cervical nodes presenting the same picture. In our
case all of the abdominal nodes were involved, including the peri-
esophageal and periaortic. In addition, the tracheobronchial nodes, on
the left side only, showed typical changes, thus nicely demonstrating
the drainage of the left bronchomediastinal trunk into the thoracic
duct. The right bronchomediastinal trunk normally empties into the
right lymphatic trunk or junction of right internal jugular and sub-
clavian veins. The variation in the extent of lymph node involvement is
not difficult to explain. When back pressure reaches a certain level in
the receptaculum chyli, it will be communicated to the lumbar trunks
and so to the retroperitoneal nodes. With the mounting tide of pres-
sure reaching the upper portion of the thoracic duct, eventually the left
bronchomediastinal trunk will be involved, at least in the instances in
which it empties directly into the thoracic duct. Although Korsch did
not specifically mention the right-sided paratracheal nodes, these could
be involved also if the disease lasts long enough, or if the obstruction
in the thoracic duct becomes sufficiently severe, by the opening of
anastomotic channels between right and left bronchomediastinal
trunks, and by subsequent backing up of accumulated fats through
these new channels.

Chylous ascites was present in our case, and in Blumgart's [2] second
case, as well as in those of Reinhart and Wilson,[5] and Sailer and Mc-
Gann.[7]

DISCUSSION

Attempts to explain the etiology and pathogenesis of intestinal lipodystrophy have been at least as numerous as the case reports; all of them, needless to say, are highly theoretical. In general, they fall into three groups: the first seeks to identify Whipple's disease with other previously described diseases; the second would incriminate a phase of fat digestion and absorption, either normal or abnormal; and the third evokes a mechanical or obstructive factor.

In the first group, sprue, local lipoid storage, and generalized lipoidoses have been enumerated most often. It is generally accepted, however, that Whipple's disease can be identified with none of these. In addition, it is worth mentioning that Whipple [1] observed in the fat vacuoles and foam cells of a mesenteric lymph node a rod-shaped body that stained only with the Levaditi technic, and that suggested to him a possible relationship between his case and the group of spirochetal diseases. Such a body has not been described since, and the positive serologic findings in Reinhart and Wilson's [5] case as well as in our own were probably entirely coincidental.

In the attempt to demonstrate that Whipple's disease is in effect an intestinal lipodystrophy, almost no phase of the mechanism of fat digestion and absorption has been neglected. It has even been suggested that the anatomic findings might represent merely a phase in normal alimentation; or of increased intake of fat or of peculiarities of diet with absorption of unusual fats. A deficiency in pancreatic lipase has been postulated. Pearse [10] incriminated bile salt metabolism. Apperly and Copley [12] felt that there was a failure in resynthesis with retention of fatty acids in the tissues. Glynn and Rosenheim, [15] whose patient clinically was thought to have Addison's disease, called attention to the evidence that adrenalectomy interferes with the phosphorylation of fats in the intestine and delays fat absorption. Finally, an increased excretion of fat into the intestines rather than a diminished absorption has been suggested.

There remains the third group of theories, which center around obstruction of the thoracic duct or of the mesenteric lymphatics. A congenital form of obstruction is unlikely in view of the age distribution of the known cases. In the few cases of intestinal lipodystrophy in which the thoracic duct was dissected, it was free of obstruction; whereas obstruction of the thoracic duct from various causes as demonstrated at autopsy or from experimental ligation in animals has not been accompanied by the characteristic morphologic changes of Whipple's disease. Furthermore, Whipple deduced, from the fact that fatty acid crystals and mast cells were present in the fluid of the duct,

that there was also no obstruction in the lymphatic radicles between the mesenteric nodes and the receptaculum. In our own case, and in others in which mediastinal and tracheobronchial nodes were involved, it seems a reasonable assumption that there was no complete obstruction, at least, either in the efferent lymphatics of the mesenteric nodes or in the thoracic duct, since apparently there was a backing up of the accumulated fatty deposits into the thoracic nodes. It must be admitted, however, that such circumstantial evidence may rule out a completely obstructive lesion, but not a partial obstruction.

Unfortunately, from all these theories we can conclude only that in Whipple's disease there exist both obstruction in the lymphatic drainage of the small intestine and interference with the absorption of fats. The crux of the matter now appears to be: which is the primary factor? If the essential disturbance is one of malabsorption, although the cause of this is still unexplained and although it may proceed from a variety of causes, Whipple's disease can be considered a distinct entity. If, on the other hand, the malabsorption is only secondary to obstruction of lymphatics, the latter also attributable to a variety of as yet unexplained inflammatory or sclerosing lesions, the entity ceases to exist. For the obstruction may be encountered in its most innocuous form incidentally at autopsy, as, for example, a xanthomatous deposit in the mesentery, thus substantiating Thannhauser's [17] theory; or, more conspicuously, as multiple cyst-like dilated lymph nodes, perhaps massive enough to have produced symptoms; or in its more malignant or end-stage, when the entire drainage of the intestinal lymphatics is partially or completely blocked.

SUMMARY

A case of intestinal lipodystrophy of Whipple is presented.

In an analysis of reports of similar cases, two not previously so designated have been included. The theoretical explanations of Whipple's disease fall into three groups: those which seek to identify it with other previously described diseases; those which implicate a phase of normal or abnormal fat digestion and absorption; those which invoke a mechanical or obstructive factor.

Attention is called to the possibility that Whipple's disease may not be a clinical or pathological entity.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 75

Fig. 1. *a*. Cross section of wall of jejunum and mesentery. Dilated lymphatics in wall of jejunum and mesentery appear as white spots and streaks. Many of the irregular white areas in the mesenteric fat are xanthomatous foci. *b*. Mucosal surface of jejunum, showing prominent valvulae conniventes and plush-like appearance. The latter is due to enlargement of the villi, which are seen in the photograph as pale dots. *c*. Serosal surface of jejunum. The dilated lymphatics appear in part as a tracery of white lines, and in part as white spots. Some of the irregular white areas are xanthomatous foci.

Fig. 2. Circular fold of jejunum, showing enlarged, bizarre-shaped villi, homogeneous coagulum in stroma of villi, and in mucosal and submucosal lymphatics, and masses of foam cells in submucosa. $\times$ 25.

A   B   C
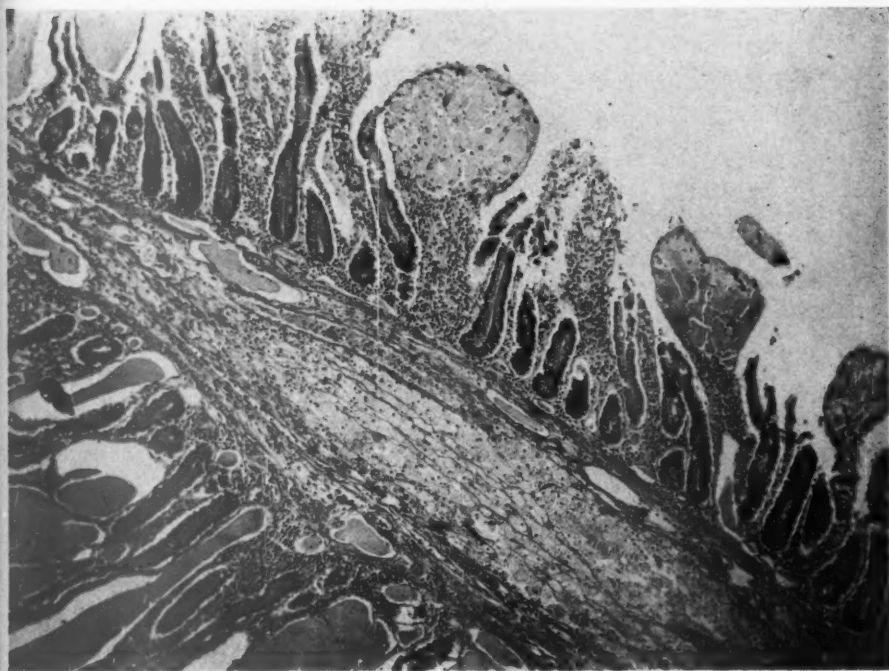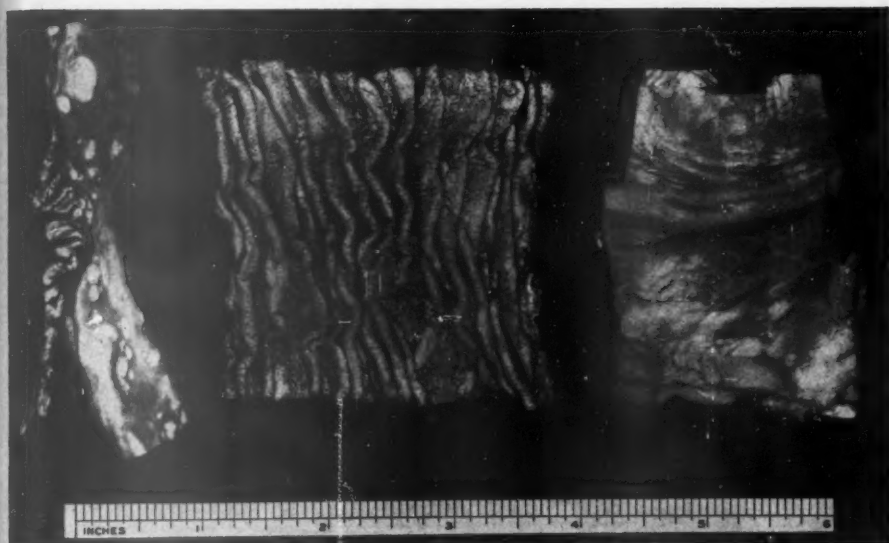
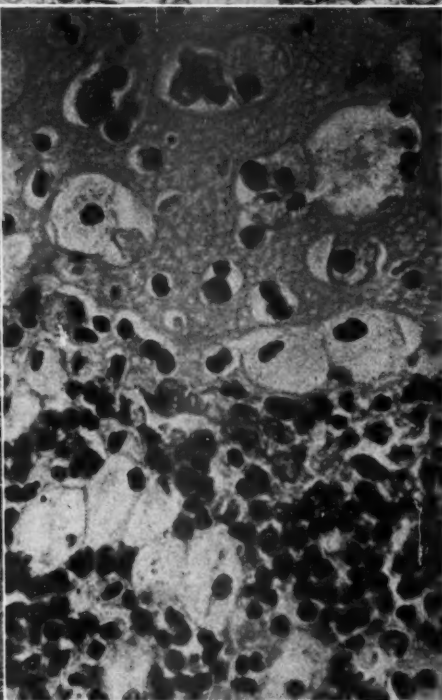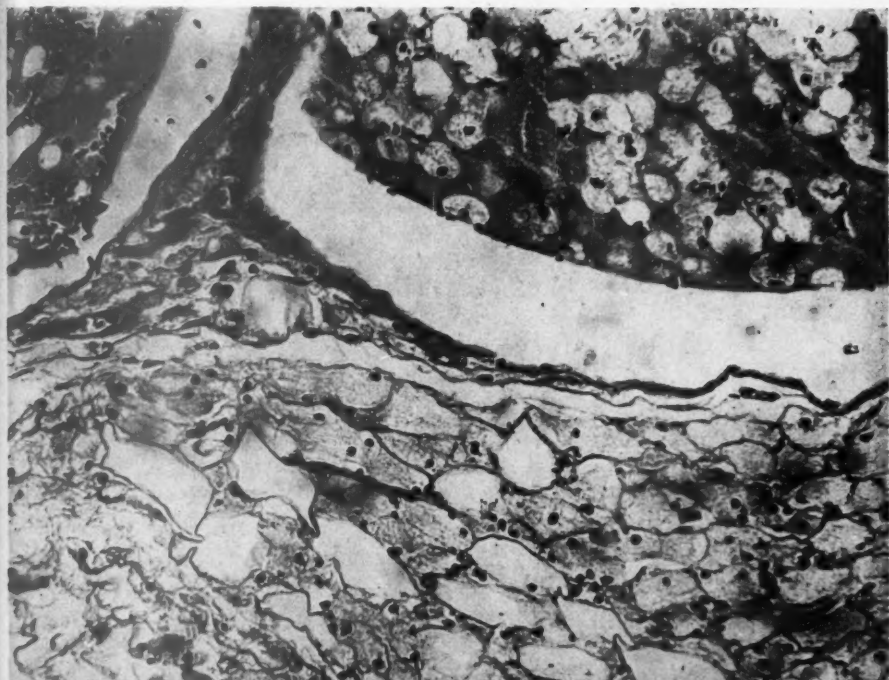Rosen and Rosen   Intestinal Lipodystrophy

FIG. 3. Mesentery. Dilated lymphatics filled with coagulum and foam cells. Accumulation of foam cells in the fat (xanthomatous focus). × 200.

FIG. 4. Tracheobronchial lymph node, showing dilated sinuses filled with coagulum and foam cells, and compressed lymphatic cords. × 50.

FIG. 5. Same lymph node as shown in Figure 4. × 400.

5

Rosen and Rosen

Intestinal Lipodystrophy

INFECTIOUS MONONUCLEOSIS
AN AUTOPSY REPORT *

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Infectious mononucleosis has come to be regarded as a fairly common disease, occurring sporadically or in small epidemics. The mortality from the disease has been almost negligible, with a resulting paucity of material for histopathologic study. The only previously reported case which was autopsied was that of Ziegler,[1] in which the patient died of a ruptured spleen in the fourth week. In this paper we wish to report the autopsy findings of a case of infectious mononucleosis in which the patient died accidentally in an airplane crash about 1 month after the onset of the acute illness.

The clinical entity of glandular fever was described by Pfeiffer [2] in 1889. In 1920 Sprunt and Evans [3] described "infectious mononucleosis," which a year later was shown to be identical with glandular fever by Tidy and Morley.[4] The heterophil or sheep cell agglutination was described by Paul and Bunnell [5] in 1932. This test, plus the description of the characteristic hematologic findings by Osgood,[6] Kracke and Garver,[7] and Downey and Stasney,[8] made possible accurate, objective laboratory diagnosis of infectious mononucleosis. The widespread use of these laboratory procedures, especially in the Armed Forces in which almost all patients with upper respiratory infections are hospitalized, has brought to light many cases of infectious mononucleosis which would ordinarily remain undiagnosed, and has led to the realization that it is a much more common disease than is generally appreciated.

The clinical features of infectious mononucleosis are protean, and the severity of the disease is xtremely variable. The more common clinical picture includes fever, malaise, headache, sore throat, lymphadenopathy, splenomegaly, skin lesions, hepatomegaly, and gastrointestinal complaints. Jaundice during infectious mononucleosis has been observed in 3 to 5 per cent of cases. Involvement of the central nervous system associated with abnormalities in the spinal fluid has been reported by Epstein and Dameshek,[9] Thelander and Shaw,[10] and Landes, Reich, and Perlow.[11] Myocardial changes during acute infectious mononucleosis have been noted by Candel and Wheelock [12]

who reported a case with electrocardiographic evidence of acute myocarditis, and by Logue and Hanson [13] who reported a case with first degree heart block.

The reason for the wide diversity of clinical manifestations becomes readily apparent from the autopsy report of Ziegler [1] and from the case to be described below. Infectious mononucleosis is a generalized disease with organic changes, as evidenced by cellular infiltration in almost every organ in the body. The clinical picture is the composite of the changes wrought in the affected organs, and will vary in type and severity with the organ system predominantly involved. The lymph nodes, spleen, and nasopharyngeal tissues appear to be the more usual sites of involvement, but changes can occur in the lungs, liver, kidneys, skin, heart, testes, adrenals, brain, and probably in other organs; and thus account for the occasional atypical or unusual cases.

The cause of the disease is still uncertain. The concept that "Bacillus monocytogenes" is the etiologic agent is no longer tenable. The general opinion is that the etiologic agent is probably a virus, although no specific virus has as yet been isolated.

The histologic features of infectious mononucleosis have been studied from surgical material and that taken for biopsy. Sprunt and Evans [3] stated that the histopathologic picture was not distinctive and may suggest one of the lymphomas. Fox,[14] in 1927, studied a tonsil and cervical lymph node and concluded that they showed nothing specific—only hyperplasia of the lymphoid elements with retention of the normal architecture. Pratt,[15] in 1931, reported the findings in two biopsies of cervical lymph nodes removed from himself a year apart; and found marked reticulo-endothelial hyperplasia in the first specimen. The second showed a similar but less marked hyperplasia, with some fibrosis. Downey and Stasney [16] studied lymph nodes from 8 cases of infectious mononucleosis taken at various stages of the disease. They noted extreme hyperplasia of both the lymphocytes and the reticulum, but never complete obliteration of the nodal architecture. They also concluded from imprint studies that the atypical lymphocytes present in the peripheral blood had their origin in the nodes. Gall and Stout,[17] in 1940, studied lymph nodes removed from 10 patients, and described a morphologic pattern which they considered characteristic of the disease. They emphasized again that the nodal architecture was preserved, although it was distorted in some cases. They described three predominant features which distinguished infectious mononucleosis from ordinary hyperplasia: first, marked proliferative activity in the pulp which tended to obscure the margins of the follicles; second, focal proliferative activity of the clasmatocytes, which simulated "epithe-

lioid cells" and formed small nodules (no necrosis or giant cells were ever noted); and third, the presence in the nodes of many "infectious mononucleosis cells." These cells they described as large, with "abundant, slightly foamy, cerulean blue cytoplasm," identical on imprint preparation and supravital staining with the characteristic cells found in the circulating blood. These cells they considered almost pathognomonic of the disease, and seen best with Zenker's fixation and the phloxine-methylene blue stain. King,[18] in 1941, reported a case of spontaneous rupture of the spleen in infectious mononucleosis. Microscopic study of the spleen and appendix removed at laparotomy revealed nothing distinctive. Straus,[19] in 1942, reported a case in which an appendix, removed during acute infectious mononucleosis, showed morphologic changes in the lymphoid tissue identical with those seen in a lymph node removed at the same time, and similar to those described by Downey and Stasney, and Gall and Stout. Darley, Black, Smith, and Good [20] reported spontaneous rupture of the spleen in infectious mononucleosis. Examination of the spleen revealed an increase in lymphoid elements and the presence of an atypical cell similar to the characteristic lymphocytes found in the peripheral blood. An additional case of traumatic rupture of the spleen was reported by Milne.[21] The preliminary microscopic diagnosis was Hodgkin's disease, but further study revealed infectious mononucleosis.

Ziegler,[1] in his report of a fatal case with autopsy, described changes in the liver, kidneys, lungs, and spleen. The lesions in the liver, kidneys, and lungs consisted of focal infiltrations of mononuclear cells, with reticulocyte proliferation and necrosis. The changes in the spleen were more diffuse than focal in character.

REPORT OF CASE *

H. S., a white, American Army Air Forces pilot, 23 years old, was admitted to a small station dispensary on about May 11, 1945, because of malaise and fever. He was kept in bed, given two "sulfa" tablets four times a day, and penicillin for 1 day before being admitted to a station hospital on May 18. He had previously been in excellent health and physical condition. Family history and previous personal history were not significant. He had had no serious illness or injury.

At the time of admission to the station hospital he was complaining of headache, and was febrile. There was no cough. Physical examination was negative. The skin was clear, and there was no significant glandular enlargement. The lungs were clear; the heart, normal. There were no signs of disease of the nervous system. Blood taken at the time of admission showed a red cell count of 4,500,000; hemoglobin, 80 per cent (Sahli); 11,450 white blood cells with 14 per cent neutrophils, 77 per cent lymphocytes, 9 per cent monocytes. The urine was negative.

A roentgenogram of the chest taken on the day after admission showed a definite increase in the vascular and peribronchial m .rkings on the right side. The hilar

* The clinical record was obtained through the courtesy of Capt. William C. Weir, M.C.

markings were also increased in prominence. In the lower aspect of the right lung an early peribronchial infiltration was noted. These findings suggested the diagnosis of primary atypical pneumonia.

Blood taken on May 22, 4 days after admission and about 11 days after the onset of the illness, showed a heterophil antibody titer of 1:896. On May 25, he complained of sore throat, was found to have a red and edematous pharynx, and was given 50,000 units of penicillin with marked improvement in the following 2 days. He was asymptomatic and afebrile after May 27.

On May 28, the white blood cell count was 10,000, with 30 per cent neutrophils and 61 per cent lymphocytes. A further report (undated) gave a differential count of 13 per cent neutrophils, 83 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils, with the remark that the lymphocytes were atypical and characteristic of infectious mononucleosis. The heterophil antibody test was repeated on May 28, and the titer was again found to be 1:896.

Roentgenograms of the lungs on May 31 showed no abnormalities. The patient was discharged to duty on June 1. On June 10, approximately 1 month from the onset of illness, and 2 weeks after the remission of clinical symptoms, he crashed while piloting an airplane, and was dead when pulled from the plane a few minutes later. Autopsy was performed 30 hours after death.

AUTOPSY FINDINGS

The gross findings were essentially those of severe trauma. There were multiple fractures of the skull and facial bones, and compound fractures of the left femur and right hand. There was a moderate amount of subdural and subarachnoid hemorrhage, and occasional petechial hemorrhages were present in the brain substance. There was also extensive pulmonary hemorrhage. The liver, spleen, kidneys, and remaining viscera were of normal size and weight, and showed no gross abnormalities, with the exception of the retroperitoneal and hilar lymph nodes, which were discrete and grossly enlarged, measuring up to 3 cm. in greatest dimension.

Microscopic Examination

All tissues except the brain were fixed in Zenker's solution; the brain was fixed in 10 per cent formalin. All sections were stained with hematoxylin and eosin.

Liver. The liver parenchyma was studded with small, discrete, focal areas of cellular infiltration (Figs. 1 and 2). Many of these infiltrates were perilobular in distribution, but just as many were scattered through the lobules with no characteristic localization. The cellular infiltrations consisted almost exclusively of rather large mononuclear cells, with oval or rounded nuclei, a few of which were reniform. Varying numbers of lymphocytes, and an occasional neutrophil, were present. Definite vacuolization of the cytoplasm of the mononuclear cells could not be made out. In the areas of infiltration the liver cells had mostly disappeared. The liver cells immediately surrounding these areas showed some degree of atrophy and no evidence of regeneration.

Kidney. Scattered throughout the renal cortex and medulla were many small, focal areas of mononuclear infiltration similar to those described above. There were atrophy, degeneration, and disappearance of the tubules in some of these areas (Fig. 4).

Heart. The heart showed a few interstitial collections of mononuclear cells and lymphocytes (Fig. 5). These collections were small to moderate in size. There was no atrophy or replacement of the muscle fibers.

Lung. There were many red blood cells, considerable edema fluid, and the usual numbers of "heart lesion" cells in the alveoli and bronchi. Many nodular collections of mononuclear cells and lymphocytes, similar to those previously described, were seen (Fig. 3). These were in relation to bronchi and blood vessels, and often within the interstitial tissues. Anthracotic pigment was present in the usual quantities in the peribronchial lymphoid tissue, but was not present in the nodules.

Testis. A moderate number of focal collections of mononuclear cells were seen within the interstitial tissue of the testis and the tunica albuginea (Fig. 6). These were quite large and were morphologically similar to those previously described. Spermatogenesis and the cells of Leydig were within normal limits.

Adrenal. There were a few foci of mononuclear infiltration present chiefly in the adrenal medulla, occasionally in the cortex and capsule (Fig. 7). These were not too unlike the lymphoid collections often found in this organ, and may not have been the result of infectious mononucleosis.

Brain. An occasional blood vessel in the cerebral cortex showed heavy cuffing of mononuclear cells, mostly lymphocytes (Fig. 8).

Spleen. The splenic architecture, follicles, and pulp were essentially normal. Moderate numbers of eosinophils were present, consistent with the sudden death. The sinusoids were prominent, and there was some proliferation of reticulo-endothelial cells.

Lymph Nodes. The nodal architecture was preserved. The sinusoids were unusually prominent, but aside from a moderate degree of hyperplasia of the reticulo-endothelial cells there was no striking abnormality.

Other Organs. Sections of aorta, pancreas, esophagus, pylorus, jejunum, ileum, appendix, urinary bladder, prostate, diaphragm, thymus, pituitary body, and costal bone marrow showed no abnormalities except for post-mortem autolytic changes. However, it is possible that if larger amounts of tissue had been preserved and more sections taken for study, additional .foci of cellular infiltration might have been encountered.

COMMENT

This patient had clinical infectious mononucleosis 2 to 4 weeks prior to death. The diagnosis was established beyond reasonable doubt by the clinical picture, hematologic findings, and the strongly positive heterophil antibody test on two separate occasions. It is therefore logical to assume that the microscopic lesions noted are those of a late stage of infectious mononucleosis. They are very similar in type and distribution to the visceral lesions described by Ziegler.[1] Unfortunately, the body was not obtained for autopsy until 30 hours after death, and had not been refrigerated during relatively hot weather. The tissue changes which ensued obscured the precise histologic details of the lesions. In addition, infectious mononucleosis was not suspected at the time of autopsy, and it was not until several weeks later that the clinical record was obtained. Had we been aware that the patient had just recovered from acute infectious mononucleosis, more careful search for lymph nodes would have been made, and special studies, such as imprint smears and supravital stains, would have been attempted.

This case emphasizes again the basic concept suggested by Ziegler[1] and others that infectious mononucleosis is a generalized disease, with lesions in many, and possibly all, organs of the body. The lesion consists essentially of a focal infiltration of mononuclear cells, including variable numbers of small lymphocytes, which in some cases crowds out and replaces the normal parenchyma. No evidence of fibrosis of the lesions was noted. It may be that the mononuclear cells are identical with the atypical lymphocytes seen in the peripheral blood and described by Gall and Stout[17] in affected lymph nodes, but we could not ascertain this from our sections.

Focal microscopic infiltrations were seen in the liver, kidneys, heart, lungs, testes, adrenals, and brain. The lesions in the adrenals are somewhat questionable, as similar collections of lymphoid tissue are frequently encountered in this organ. It is quite remarkable that the lymph nodes and spleen, which are usually most profoundly affected in infectious mononucleosis, were in this case relatively uninvolved. It is possible that in this particular case these organs were less involved than usual, or that they returned to normal more rapidly than other tissues.

The lungs are of considerable interest in this case. On the basis of the roentgenologic evidence, a tentative diagnosis of "primary atypical pneumonia, etiology unknown" was made—the nomenclature used in the Army to label so-called "virus" pneumonia. Since this patient did have definite clinical infectious mononucleosis at the time the roent-

genogram was made, it is possible that the nodular infiltrations in the lungs were those of infectious mononucleosis, rather than of a less likely co-existing independent disease involving the respiratory tract. It may very well be that infectious mononucleosis can produce a clinical and radiographic picture simulating "virus" pneumonia, as has been suggested by Halcrow, Owen, and Rodger.[22]

The brain in this case presented the first opportunity, to our knowledge, to study sections of the central nervous system in infectious mononucleosis. As mentioned previously, clinical involvement of the central nervous system, with spinal fluid changes, has been reported several times. Histologic study of the brain in this case, which had no clinical symptoms referable directly to organic changes in the central nervous system, revealed a few blood vessels, chiefly in the cortex, with perivascular infiltrations of lymphoid tissue. The histologic picture was similar to that seen in mild virus encephalitis. It thus appears likely that the central nervous system shares with the other viscera the generalized involvement in infectious mononucleosis.

Histologic changes in the heart in infectious mononucleosis have not been described previously, but have been postulated on the basis of electrocardiographic findings. The interstitial infiltrations seen in the heart in this case are compatible with conduction changes demonstrable by electrocardiograms, assuming that the infiltrations may occur in any part of the cardiac muscle and may involve important conduction fibers.

The presence of microscopic infiltrations in the liver and kidneys furnishes the organic background to explain those occasional cases of infectious mononucleosis in which "hepatitis" or "nephritis" dominates the clinical picture. It is probable, due to the diffuse nature of the disease, that these organs are involved to some degree in almost every case, although rarely with sufficient alteration of function to be clinically detectable.

SUMMARY

Necropsy was done in a case of infectious mononucleosis, in which the patient had died 2 to 4 weeks after the acute illness as a result of an accident. Focal cellular infiltrations, similar to those previously described in infectious mononucleosis, were found in the liver, kidneys, heart, lungs, adrenals, testes, and brain. Cerebral and cardiac lesions, not previously described, were found.

This case emphasizes again that infectious mononucleosis is a generalized disease, and may produce organic changes in many viscera, thus explaining the wide diversity of clinical manifestations which are encountered.

It is suggested that infectious mononucleosis may produce a clinical and radiographic picture simulating "primary atypical pneumonia."

We are indebted to Mr. John Carabitses, Children's Hospital, Boston, for the photomicrographs.

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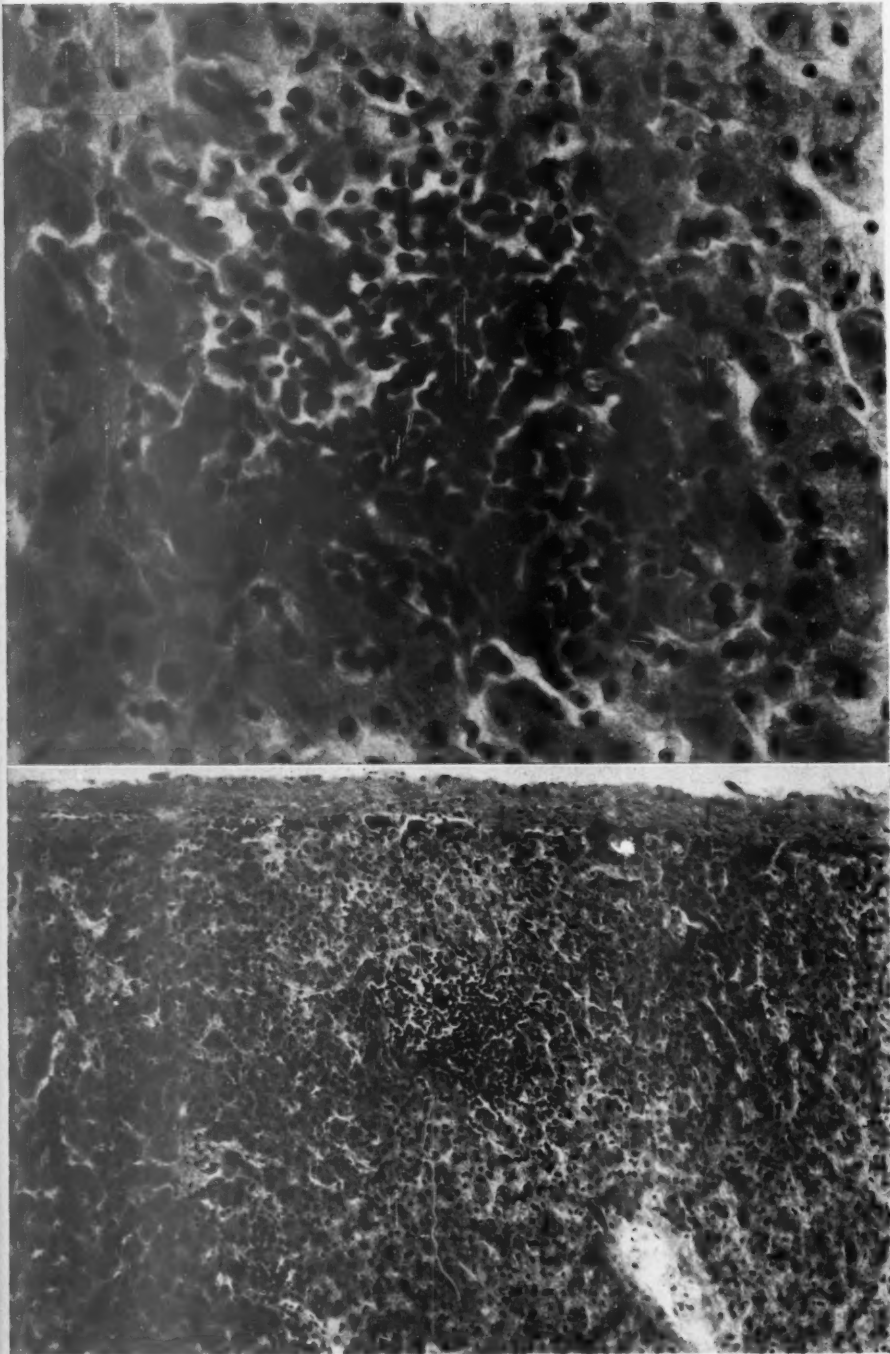
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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 77

All sections were stained with hematoxylin and eosin. $\times$ 120 except for Figure 1.

FIG. 1. Liver, high power. Focal mononuclear infiltration, with replacement of liver cells. $\times$ 450.

FIG. 2. Liver, low power. Focal collections of mononuclear cells.

Allen and Kellner

Infectious Mononucleosis

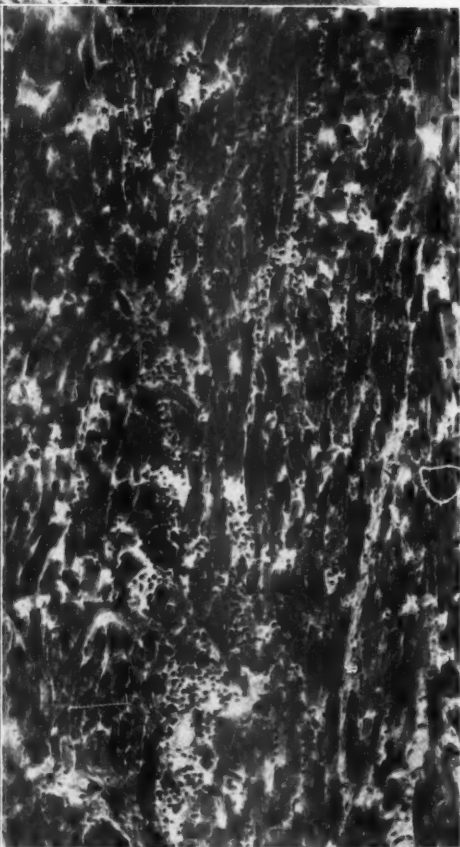FIG. 3. Lung, low power. Nodular perivascular and interstitial infiltrations of mononuclear cells.

FIG. 4. Kidney, low power. Mononuclear infiltrate in the cortex, with atrophy and replacement of the renal tubules.

FIG. 5. Heart, low power. Interstitial infiltration of mononuclear cells.

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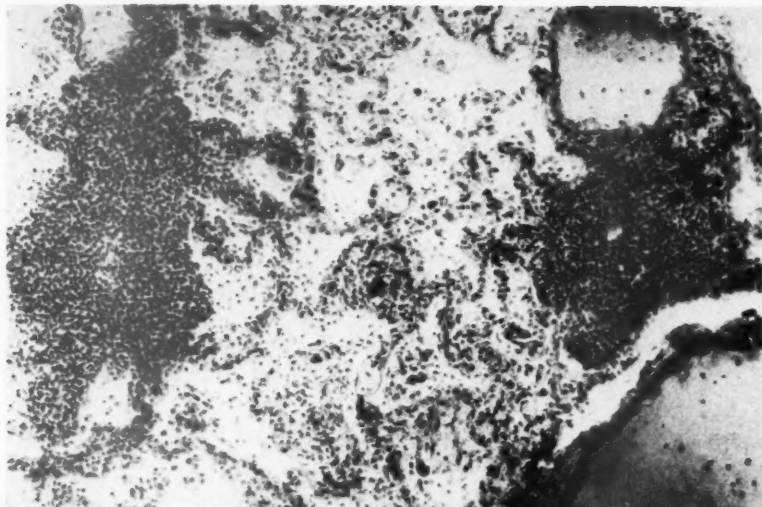
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Allen and Kellner   Infectious Mononucleosis

PLATE 79

FIG. 6. Testis, low power. Focal interstitial infiltration of mononuclear cells.

FIG. 7. Adrenal, low power. Focal infiltration of mononuclear cells in medulla.

FIG. 8. Brain, low power. Cortical vessel with perivascular cuff of mononuclear cells.
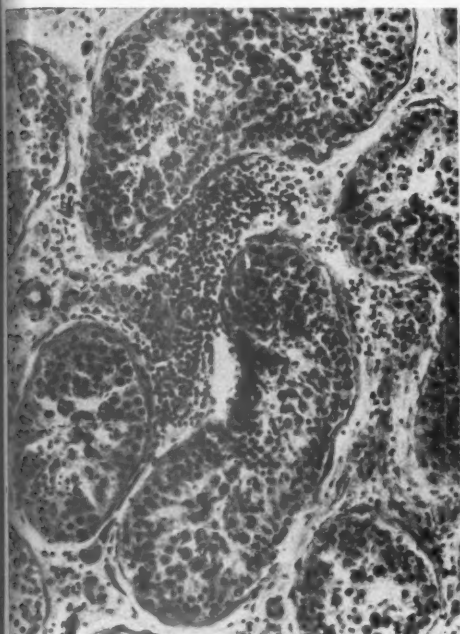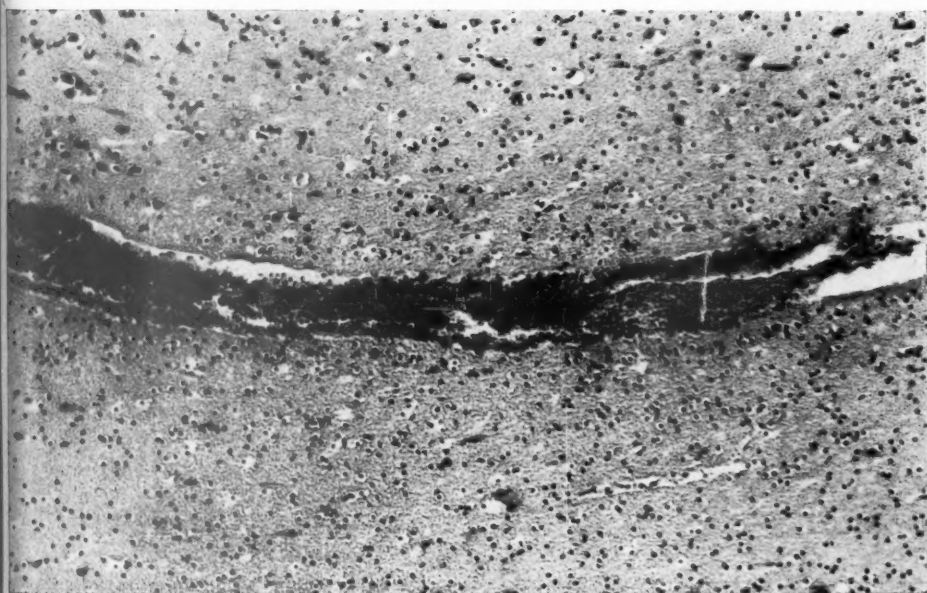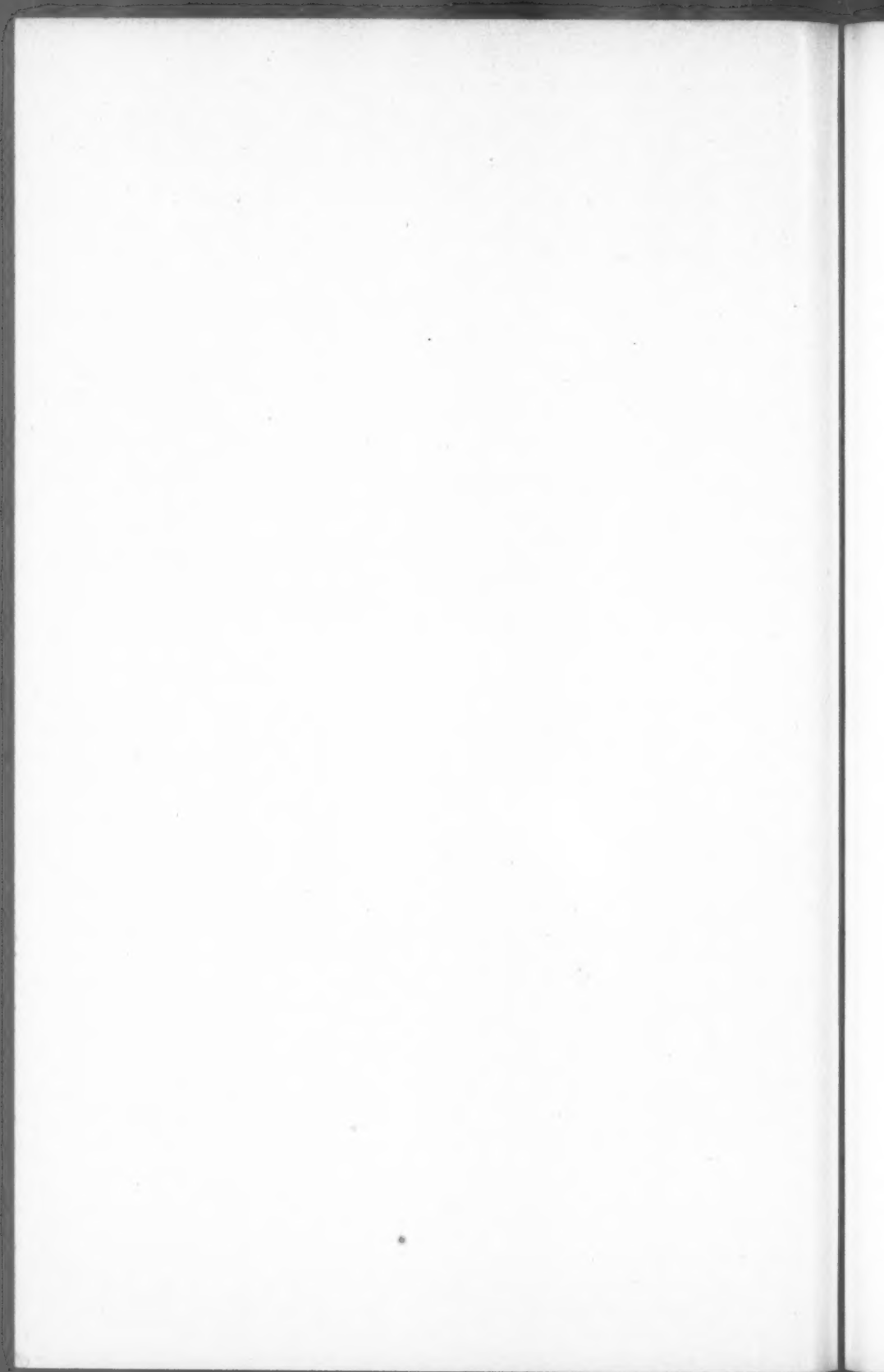
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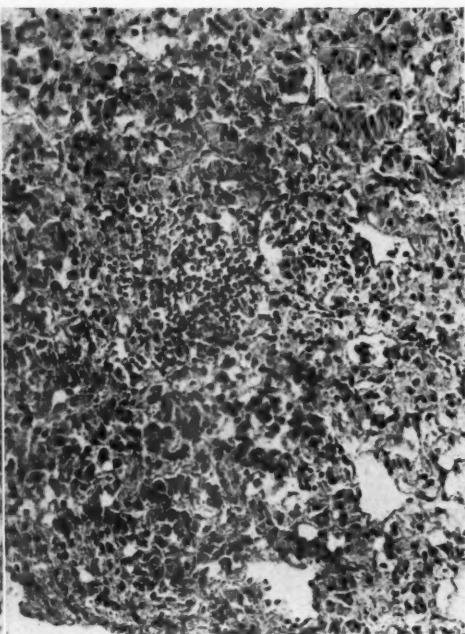
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Allen and Kellner   Infectious Mononucleosis

CYSTS OF THE ADRENAL GLAND WITH CASE REPORT *

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In the past 20 years only four papers on adrenal cysts have appeared in American literature. As there is a scarcity of material on this subject, this report is believed to be justified.

The mechanism by which adrenal cysts are formed does not coincide with the manner in which true retention or inclusion cysts are developed. They result usually from ectasia of pre-existing vessels [1] or cystic degeneration of hematomas or adenomas.[2] Therefore, they are better called pseudocysts.

A classification of these lesions by Levison [3] includes true glandular cysts, cystic adenomas, cystic lymphangiomas, pseudocysts, and echinococcus cysts. The first two classes are excluded from this paper because satisfactory reports and descriptions were not found in the literature. Echinococcus cysts of the adrenal gland are exceedingly rare. From a study of 1,617 cases of echinococcosis by Barnett,[4] it was shown that the adrenal gland is involved in much less than 0.5 per cent. Dew,[5] in his exhaustive monograph, cited only a single case of echinococcus disease involving the adrenal gland and in this the lesion occupied a position in the capsule.

It also has been suggested that cysts of the adrenal glands are of a secondary nature. According to Rabson and Zimmerman,[1] cystic lymphangiomas of the adrenal gland should be classed more accurately as lymphangiectasias. They concluded that lymphangiomas and hemangiomas are rare in the suprarenal body and that hamartomas are the most common cystic lesions seen in the adrenal gland. In this category the cases of Ballance [6] and of Rabson and Zimmerman may be included. Degeneration of hematomas resulting in pseudocyst formation was exemplified by the cases of Iglitsyn,[2] Pearse,[7] and most probably by that of Levison.[8]

Cysts of the suprarenal gland manifest themselves clinically in insidious and varied ways. That in the case of Rabson and Zimmerman [1] and the one recorded in this paper were found at autopsy and had apparently caused no disturbances during life. In the case reported by Ballance,[6] the patient, a 49-year-old white female, complained of sense of pressure, "indigestion," and back pain which passed around to the epigastrium. This complaint had existed for 5 years. The cyst in this case was externally palpable. Acute abdominal pain, shock, and palp-

able tumor which became apparent over a 3-day period were seen in a case reported by Pearse.[7] An erroneous diagnosis of "gallstones" and "pleurisy" had been made in this case. Levison's [3] patient manifested a pluriglandular syndrome which led to impressions of parathyroid and thyroid dysfunctions.

The gross appearance of adrenal cysts varies as does the pathogenesis. Those cysts resulting from ectasia of lymph channels consist of numerous locules that contain clear or milky fluid. The compartments reportedly may vary from 1 to 13 mm.[1] Cysts measuring 23 by 15 cm. and containing 1¼ liters of fluid have been reported.[6] The walls of the lymphangiectatic cysts are delicate and smooth.

The hematocysts have irregularly pigmented walls which may contain foci of calcareous material.[3] This is true whether the hematocysts develop in normal adrenal gland or adenomatous areas. Cysts of this type may contain bloody or reddish brown fluid. Ballance [6] cited the case of Doran in which the cyst contained 250 cc. of bloody fluid and that of Hartwell in which the cyst contained 3 liters of reddish brown fluid.

The following case is an example of lymphangiectasia of the adrenal gland.

REPORT OF CASE

M. R. (U. H. no. 86984), was a white female, 58 years of age, who was admitted with complaints of generalized abdominal pain, nausea, and vomiting of 8 days' duration. Physical and roentgenologic examinations of the abdomen led to a correct diagnosis of periappendicular abscess with partial intestinal obstruction. The chemical findings in the blood were normal with the exception of a decreased plasma chloride level and moderate hypoproteinemia. There was no clinical evidence of endocrinopathy.

Operative drainage of the abscess was undertaken. Postoperatively, the patient continued to suffer the effects of peritonitis. Treatment with penicillin and sulfonamide compounds effected no improvement. The patient died on the 14th postoperative day.

The findings at autopsy were consistent with the clinical diagnosis. The cystic right adrenal gland could in no way be related to the antemortem condition of the patient. The left adrenal gland was normal.

The right suprarenal body measured 7 by 2.4 cm. Cysts were externally apparent. On section the medulla was seen to contain smooth-walled cysts which ranged from 1 to 13 mm. in diameter. The fluid within the cysts was clear when fresh but became opaque and jelly-like in 10 per cent formaldehyde. There was no gross evidence of hemorrhage. The cysts had obviously distended the overlying cortex. Outside the walls of the larger cysts bits of compressed adrenal cortex were seen.

Microscopically, the cysts appeared as widely dilated spaces lined by

endothelium and filled with acellular, eosinophilic albuminous precipitate. Connective tissue separated the cysts. Calcareous deposits were present in the fibrous areas. The surrounding adrenal cortex showed pressure atrophy. In the better preserved portions of the cortex, glomerular, fascicular, and reticular zones could be discerned. The cortical cells were pale, granular, shrunken, and poor in lipoid material.

SUMMARY

Cysts of the adrenal glands are exceedingly rare. The most commonly reported types are hematocysts and lymphangiectatic cysts. A case of lymphangiectatic cysts of the right adrenal gland is reported.

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[*Illustrations follow*]

DESCRIPTION OF PLATE

PLATE 80

FIG. 1. This photograph shows cross sections of the lymphangiectactic cystic adrenal. The largest cyst is seen in the upper pole of the adrenal gland pictured on the left. Many smaller cysts filled with mucinous material are seen in the midportion, and normal adrenal cortex is seen in the lower portion of the same section.

FIGS. 2 and 3. Endothelium-lined spaces filled with precipitated albuminous material are shown with recognizable adrenal cortex. Hematoxylin and eosin stain. × 100.
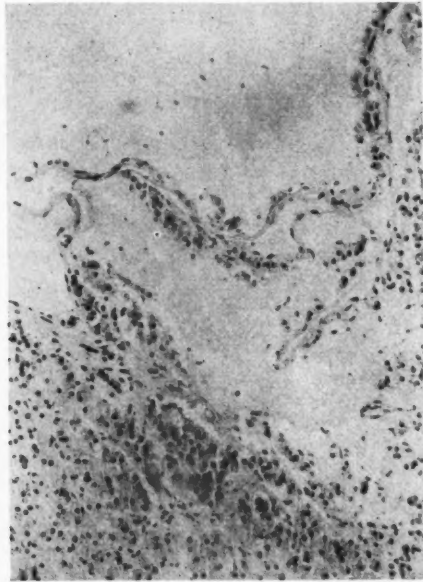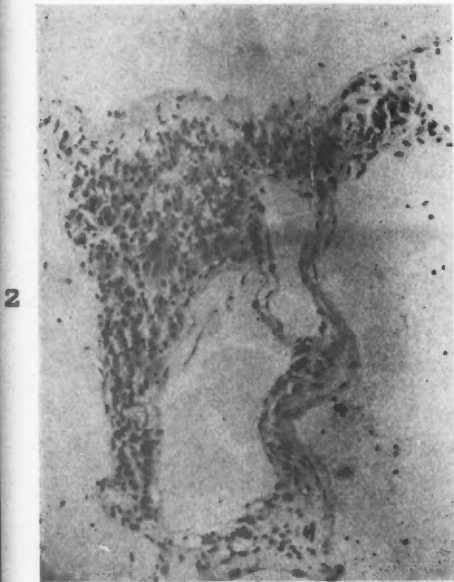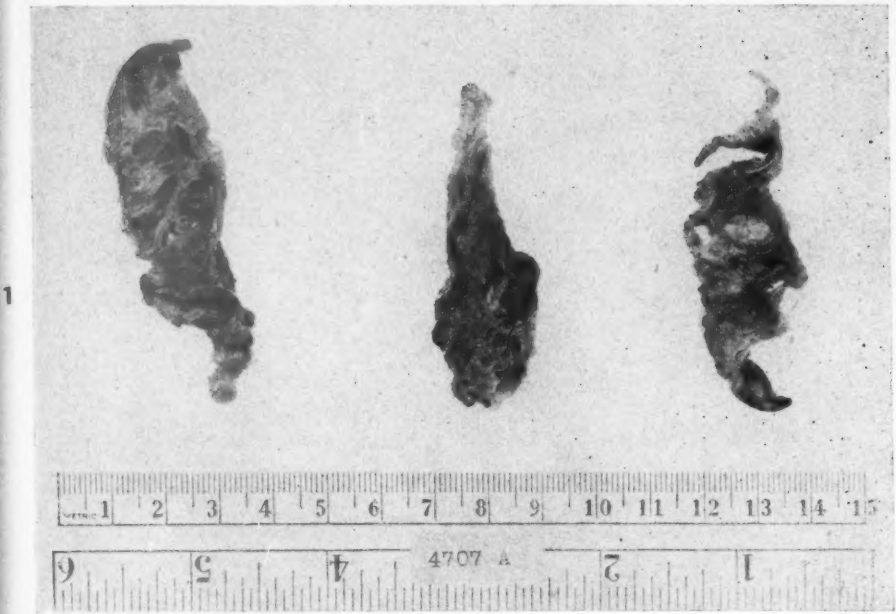
Reimann and Guyton   Cysts of the Adrenal Gland
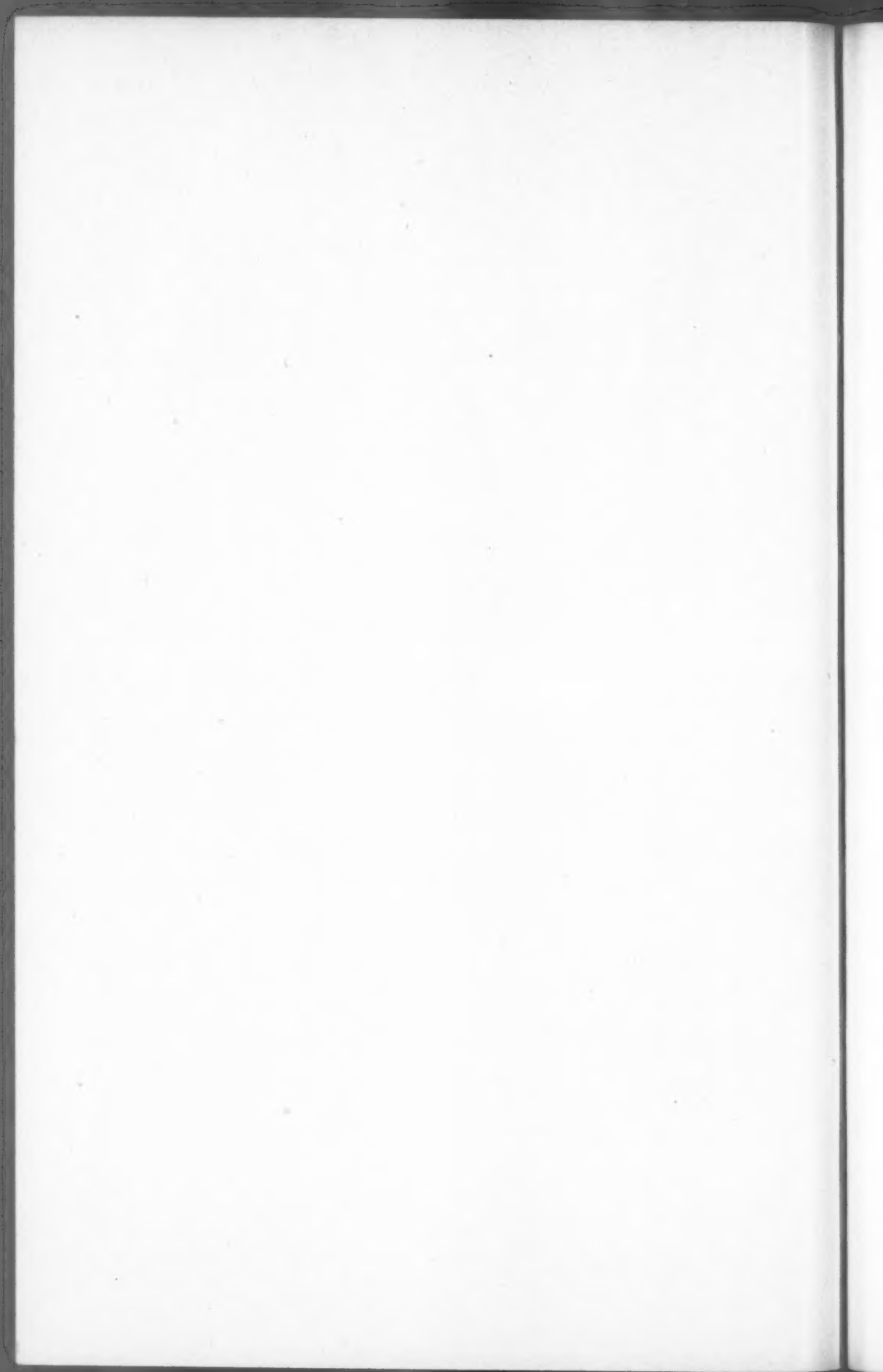
THE PATHOGENESIS OF POLYCYSTIC PANCREAS
RECONSTRUCTION OF CYSTIC ELEMENTS IN ONE CASE *

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Polycystic disease of the pancreas has not been recognized at autopsy so frequently nor studied so widely as polycystic disease of the kidney. Although variation in the character and distribution of the lesions is great, "fibrocystic disease" of the pancreas, as it is often called in the pediatric literature, is a well recognized entity in infancy. Essentially the pancreatic ducts are characteristically distorted and segmented. Some of the segments are atrophic, others are dilated and cystic. Many of these cysts may be isolated. The main pancreatic duct may or may not be atretic. Much of the glandular tissue is atrophic or is replaced by proliferating fibrous tissue and scar tissue accompanied by varying amounts of acute and chronic inflammatory exudate. The amount of fibrous stroma is often greater than is the case in polycystic disease of other organs. Squamous metaplasia of the ducts of varying degrees is often observed. Although some of the ducts are dilated and cystic, the disease is rarely characterized by diffusely distributed and large cysts. For this reason, it has not always been clear to authors reporting such cases that the disease is similar to polycystic disease of other organs. Yet the frequent association of cystic fibrosis of the pancreas with polycystic disease of the kidney, liver, and lung indicates that the lesions are essentially identical in etiology if not in morphology.

When the lesions are manifest in infancy, steatorrhea and malnutrition are often conspicuous symptoms, and are evidently the result of deficiency or absence of the external secretion of the pancreas. Since the disturbances of metabolism are usually profound and fatal, the early death of most of these children probably accounts for the rarity of extensive polycystic lesions of the pancreas in adults.

The clinical importance of polycystic disease of the pancreas was reviewed by Andersen,[1,2] and additional reports more recently have been made by Rauch, Litvak, and Steiner,[3] Oppenheimer,[4] Robbin and Bernhard,[5] Wolman,[6] Daniel,[7] Snelling and Erb,[8] Kennedy and Baggenstoss,[9] and Menten and Middleton.[10] Although the etiology of the

lesions is discussed, these papers are concerned more with the clinical aspects of the disease and the frequently associated cystic lesions of the lung than with pathogenesis. In the past, however, careful microscopic studies to determine the cause of the lesions have been made, but agreement on the pathogenesis is lacking. Reviews of the earlier literature may be found in the papers of Sears,[11] Teuscher,[12] Bartoli,[13] Rümler,[14] and Pazzagli.[15]

In general, like polycystic liver, the polycystic lesions of the pancreas have not been so thoroughly studied by means of models as have those in the kidney. The various theories of causation suggested for polycystic kidney have also been proposed for the congenital lesions of the pancreas. By some, therefore, it is held that chronic inflammation and proliferation of fibrous tissue is the fundamental lesion and causes obstruction, segmentation, and cystic dilatation of the pancreatic ducts. Although inflammation is almost always present in the polycystic pancreas, there are many cases of polycystic liver and kidney in which it is absent. By others it is assumed that failure of the two anlagen of the pancreas properly to unite may cause obstruction of the proliferating ducts and cystic dilatation of the segments. Functionally and anatomically, however, these anlagen are not analogous with those of the kidney. In addition, the theory fails to explain the occurrence of polycystic lesions of the liver and lung which are not formed by the fusion of separate anlagen. Finally, the most commonly held theory among the older German writers is the concept of Albrecht [16] that an abnormal tumorlike proliferation of epithelial and fibroblastic tissue results in faulty development of the organ. Although in many instances of polycystic disease the epithelium and fibrous stroma may have the appearance of excessive proliferation, there is nothing characteristically neoplastic about the tissue.

A different approach to the problem of polycystic disease was that of Kampmeier [17-20] and McKenna and Kampmeier [21,22] who demonstrated that the first generations of nephrons in the normal kidney are provisional and who suggested that persistence of these provisional elements would explain the occurrence of polycystic kidneys. Recently, cystic disease of the kidney and liver were studied by Norris and Herman [23,24] and Norris and Tyson,[25] respectively. By means of serial sections and reconstructions it was demonstrated that the general development of organs in the presence of polycystic disease is remarkably normal and continued normal differentiation of many epithelial elements occurs simultaneously with distortion, segmentation, and cystic dilatation of others which are fully formed. This observation suggests that a "hamartoma" is not the fundamental cause and that defects occur only after the structural units of an organ are differentiated. In the kidney

it was not determined whether the segmentation was confined to the collecting ducts or included the uriniferous tubules as well. In the liver, however, only the small intrahepatic bile ducts were segmented and cystic. It was concluded that, since early generations of nephrons and intrahepatic bile ducts normally become segmented and then are resorbed, polycystic disease is an extension of this normal process of degeneration which includes a greater number of elements than normally. Instead of complete resorption, however, many of the epithelial segments persist to form the isolated cysts of polycystic disease. The cause of this abnormality is still problematical.

In continuance of the study of polycystic disease, we have reconstructed elements of a cystic pancreas in order to determine whether this theory is also applicable to other organs. This pancreas is from case 2 previously reported by Norris and Herman [24] and Norris and Tyson [25] in which case the kidneys and liver were also cystic. Although there were no dilated cysts in the kidney, liver, or pancreas, this case has been selected as previously indicated because it is believed that the lesions represent an early stage of polycystic disease and that a proper evaluation of the essential defect can be obtained only by a study of the disease in its incipiency.

MATERIALS AND METHODS

Briefly, the patient was a full-term infant who died 24 days after birth following the onset of a hemorrhagic diathesis, jaundice, and evidence of renal failure. Sixth digits of both hands were amputated after delivery. In the preceding papers [24,25] the clinical history, anatomic diagnosis, and pathologic findings in the kidneys and liver were described and will not be repeated. Only the gross and microscopic lesions of the pancreas will be presented at this time.

The tissues were fixed in Kaiserling's and Regaud's solutions. Blocks were embedded in paraffin and sections were stained with Delafield's hematoxylin and eosin. Sections for ordinary study were cut at 5μ. In addition, several hundred serial sections, 15μ in thickness, were cut at right angles to the long axis of the pancreas from three blocks about 2 cm. on a side. These were taken from the head, body, and tail, respectively. The cystic pancreatic ducts were traced and studied microscopically in the serial sections and some of them were reconstructed by the method previously described.[23]

GROSS EXAMINATION

At autopsy the pancreas was not weighed or measured but was described as uniformly enlarged. The contours were entirely normal and the position of the organ in the body was normal. On section, the main

pancreatic duct and its orifice were not identified. Only scattered, small, irregular, tubular and cystic ducts were present in the stroma. The parenchyma was fibrous, pale, and slightly mottled. There were no large cysts.

Microscopic Examination

In blocks from the head, body, and tail, the microscopic findings were similar. There were scattered lobules of acini, which were normally formed and were frequently located at the periphery of the pancreas. Individually the epithelial cells were smaller than is normal and appeared atrophic. Nearly all of the small pancreatic ducts in these areas were irregular and slightly dilated. Many of them contained inspissated débris resembling coagulated protein. The ducts were lined by single layers of flattened or cuboidal epithelium (Fig. 1). The epithelium of some of the ducts was duplicated and some showed varying degrees of squamous metaplasia. In other areas, the ducts were not associated with acini and were completely surrounded by dense fibrous stroma (Fig. 2). Invariably these ducts were distorted and irregularly dilated. The main pancreatic duct was not identified. The extent of these areas may be more readily appreciated in a low-power photomicrograph (Fig. 3). Few islets of Langerhans were seen. Those which were present were normally formed, but also appeared shrunken and atrophic. Like some of the ducts, many of them were isolated from any glandular tissue and were embedded in fibrous stroma. All of them, however, were in the vicinity of pancreatic ducts (Fig. 4). The fibrous stroma was compact and rarely was associated with fatty tissue except about the periphery of the pancreas. Blood vessels were numerous but were arranged in no definite pattern. Inflammatory exudate was scanty. Only a few lymphocytes, plasma cells, and mononuclear phagocytes were seen and these were usually scattered (Fig. 2).

In serial sections, the larger ducts varied greatly in contour and diameter. Although there were numerous zones of constriction between areas of dilatation, most of the ducts extended for considerable distances before ending blindly. There were, however, numerous blindly-ending outpocketings approximately at right angles to the main axes of the larger ducts. Some of these were pointed, others were blunt and bulbous. Many had multiple blindly-ending branches. These resembled branches of the larger ducts, but were atypical in arrangement and were irregularly distributed. Near the larger ducts were many completely isolated but undilated cysts which appeared to be pinched-off segments of the smaller branches of the ducts (Fig. 2). A segment of one of the larger ducts showing the characteristics described has been reconstructed and is illustrated in the model (Fig. 5).

DISCUSSION

According to Lewis,[26] the human pancreas is normally formed from two separate anlagen, the ventral and dorsal pancreases, which arise from the duodenum and which are present in embryos of 3 to 4 mm. They are still separated at 10 mm. by the portal vein, but at 16 mm. are united and partly surround the vein. With the elongation of the common bile duct, the ventral pancreas becomes completely separated from the duodenum and forms part of the head and much of the uncinate process. The dorsal pancreas forms the rest of these structures and the entire body and tail. The main ducts of the dorsal and ventral pancreases unite by a single anastomosis and only rarely are there any anastomoses between their branches. The main duct of the mature pancreas, formed by this anastomosis, empties into the common bile duct and is called the duct of Wirsung. The proximal portion of the duct of the dorsal pancreas, which arises from the duodenum, may persist as an accessory duct and is called the duct of Santorini. At first the newly formed main duct is a simple wide and hollow tube having numerous radial, pear-shaped buds and branches. These become canalized and continue to subdivide. The glandular epithelium is later differentiated into mature acini. The islets of Langerhans appear in the body and tail at 54 mm. but are not present in the head until a later period. At first they are connected with the ducts by epithelial stalks. In later stages they become detached from the epithelial tubes and remain isolated thereafter.

It is not clear whether early generations of pancreatic ducts are normally provisional as are early generations of nephrons and intrahepatic bile ducts. Since isolation of epithelial ducts by segmentation is a normal process of embryologic degeneration in other organs, it is quite possible that this process may at times occur in the normal fetal pancreas.

In the present case, although slightly and diffusely enlarged, the pancreas was remarkably normal in contour and in position. A main duct was not distinguished either grossly or microscopically. The small ducts illustrated in Figures 2 and 3 were not parallel with the long axis of the pancreas but formed angles of at least 45° with it. This angle is evident in the reconstruction, in which the vertical axis of the illustration corresponds with the long axis of the pancreas (Fig. 5). Because of their number, size, and position it is thought that these ducts were large branches of the main duct which was no longer present. Although glandular tissue was lacking in much of the pancreas, when present the acini were normally formed and differentiated and were often situated at the periphery of the organ (Fig. 1). The

number of the islets of Langerhans was definitely less than is normal, but even when completely isolated in fibrous stroma the configuration was normal although the cells individually were often shrunken and atrophic (Fig. 4).

As in the kidneys and livers previously reported,[23-25] the normal gross structure of the pancreas implies that the early development of the organ was normal and that differentiation of the components continued normally for a considerable time. It is very likely that the main duct was originally present, but disappeared, probably as the result of segmentation and resorption, following the proliferation of many of its branches. These branches persisted as the numerous, small, irregular ducts, in turn with the distorted outpocketings or branches which are illustrated. It may also be assumed that normal proliferation and differentiation of the glandular tissue occurred simultaneously with segmentation and resorption of the main duct. The process of segmentation and resorption did not stop with the main duct but also involved the smaller ducts and their branches. As a result the glandular tissue became isolated and much of it atrophied and disappeared. Although isolated, some of the islets of Langerhans also persisted. Simultaneously, the degenerating epithelial elements were replaced by proliferating fibrous tissue so gradually that the gross structure of the pancreas remained normal.

If this recapitulation is correct, then the sequence of anatomic changes in the epithelial structures of the pancreas is identical with that which has been postulated for polycystic disease of the kidney and liver. Persistence of many of these isolated segments as gradually enlarging cysts can explain the lesions of polycystic disease in later life. It may be concluded, therefore, that the changes described in the pancreas of the present case are consistent with the theory that in polycystic disease the fundamental defect is segmentation of epithelial tubules and ducts after their formation in accordance with the normal architecture of the organ.

Although the process of segmentation and resorption of the ducts appears to be similar to that which occurs in the polycystic kidney and liver, the greater reduction in the glandular tissue and the much greater amount of fibrous stroma in the pancreas require further comment. It may be argued that the amount of epithelium in the anlagen was deficient from the beginning and that the extensive zones of fibrosis merely represent a condensation of fetal mesenchyma in those areas normally occupied by glandular tissue. This hypothesis seems unlikely, however, since, in contrast to the kidney, in the pancreas both the

glandular tissue and ducts are derived from the same anlage and there appears to be no deficiency of the smaller ducts in the present case. Furthermore, if the epithelial anlagen were actually deficient, the grossly normal development which was found in the pancreas of the present case hardly could have occurred. It may be argued that chronic inflammation of the pancreas, associated with contraction of fibrous tissue, may have constricted many of the pancreatic ducts and led to segmentation and resorption. This hypothesis is supported by the fact that chronic inflammatory exudate has often been reported as extensive. Such a process, however, if actually significant, would almost certainly lead to distortion of the gross structure of the pancreas. The signs of inflammation in the present case were minimal, and it has been previously emphasized by us that inflammation is frequently inconspicuous in polycystic disease of other organs. Consequently, although inflammation may contribute to the segmentation and resorption of epithelial elements in certain cases, it does not appear to be a primary factor in the pathogenesis of polycystic disease.

SUMMARY AND CONCLUSIONS

1. The polycystic lesions of the pancreas in an infant were studied by the usual methods and by a three-dimensional model which is illustrated.

2. The characteristic progressive distortion, cystic dilatation, and segmentation of the ducts are thought to have occurred simultaneously with replacement fibrosis and did not prevent the normal gross development of the pancreas.

3. It is believed that the changes described correspond with those postulated for the polycystic lesions of the kidney and liver, and indicate that in polycystic disease epithelial tubules and ducts are formed in accordance with the normal architectural pattern of the organ but then become distorted and segmented. Instead of complete resorption of these segments, as occurs in the normal degeneration of the mesonephros and in early generations of tubules of the metanephros and liver, many of them persist to form isolated cysts.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 81

FIG. 1. The pancreatic acini are normally formed, but the small ducts are distorted and cystic. Hematoxylin and eosin stain. × 105.

FIG. 2. A medium-sized duct is distorted and is completely surrounded by dense fibrous stroma. At the left, the duct-like structures are in reality small cysts which may be pinched-off branches of the larger duct. Hematoxylin and eosin stain. × 180.

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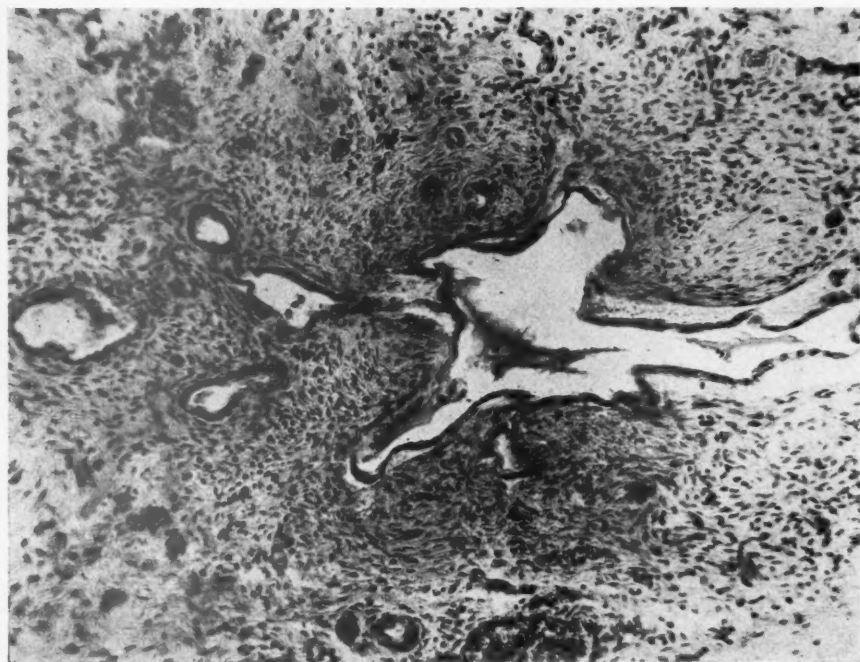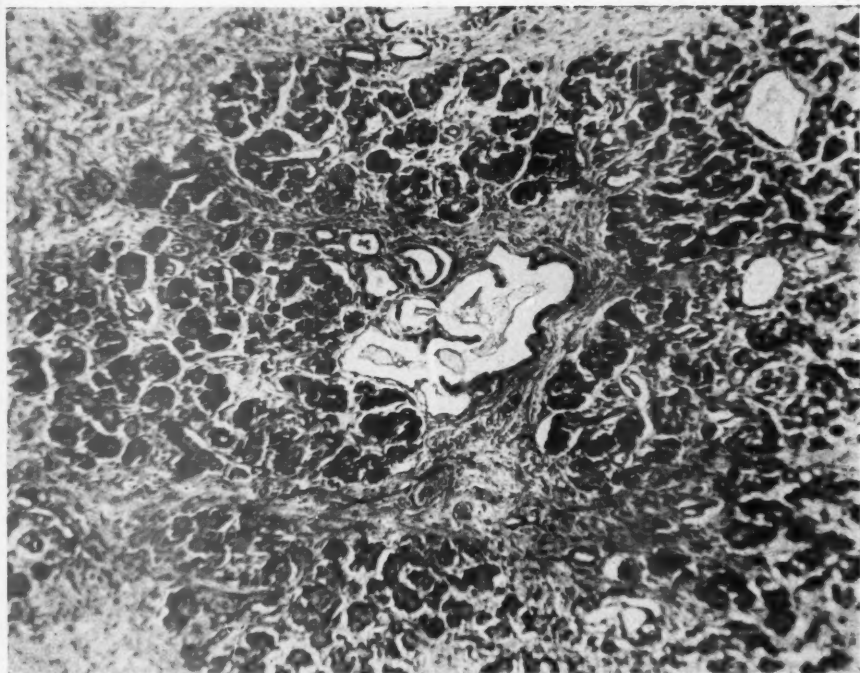
Norris and Tyson   Pathogenesis of Polycystic Pancreas

FIG. 3. In large areas, the pancreatic ducts and their branches are surrounded only by fibrous stroma. Hematoxylin and eosin stain. × 50.

FIG. 4. In the center of the field, three islets of Langerhans embedded in fibrous stroma are normally formed, but the epithelial cells are individually shrunken and atrophic. Hematoxylin and eosin stain. × 105.

3

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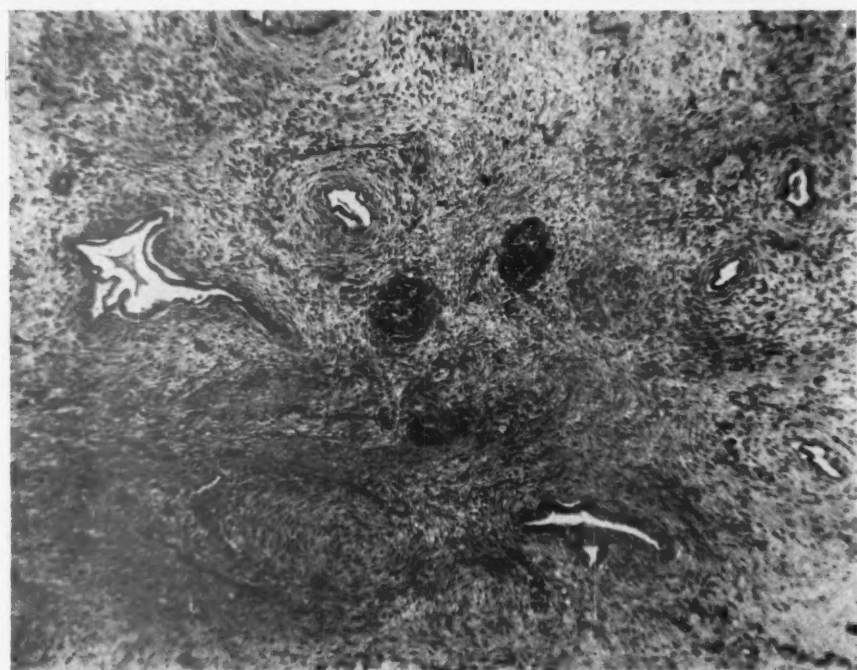
Norris and Tyson   Pathogenesis of Polycystic Pancreas

FIG. 5. The model of one of the larger pancreatic ducts shows the marked irregularity and focal dilatation. There are numerous branches, some pointed and others bulbous. To the left and above the main duct are several isolated, undilated cysts which may be pinched-off segments of some of the branches. The vertical extent of the reconstruction in the pancreas was 0.68 cm.

Plate 83

5

Norris and Tyson

Pathogenesis of Polycystic Pancreas
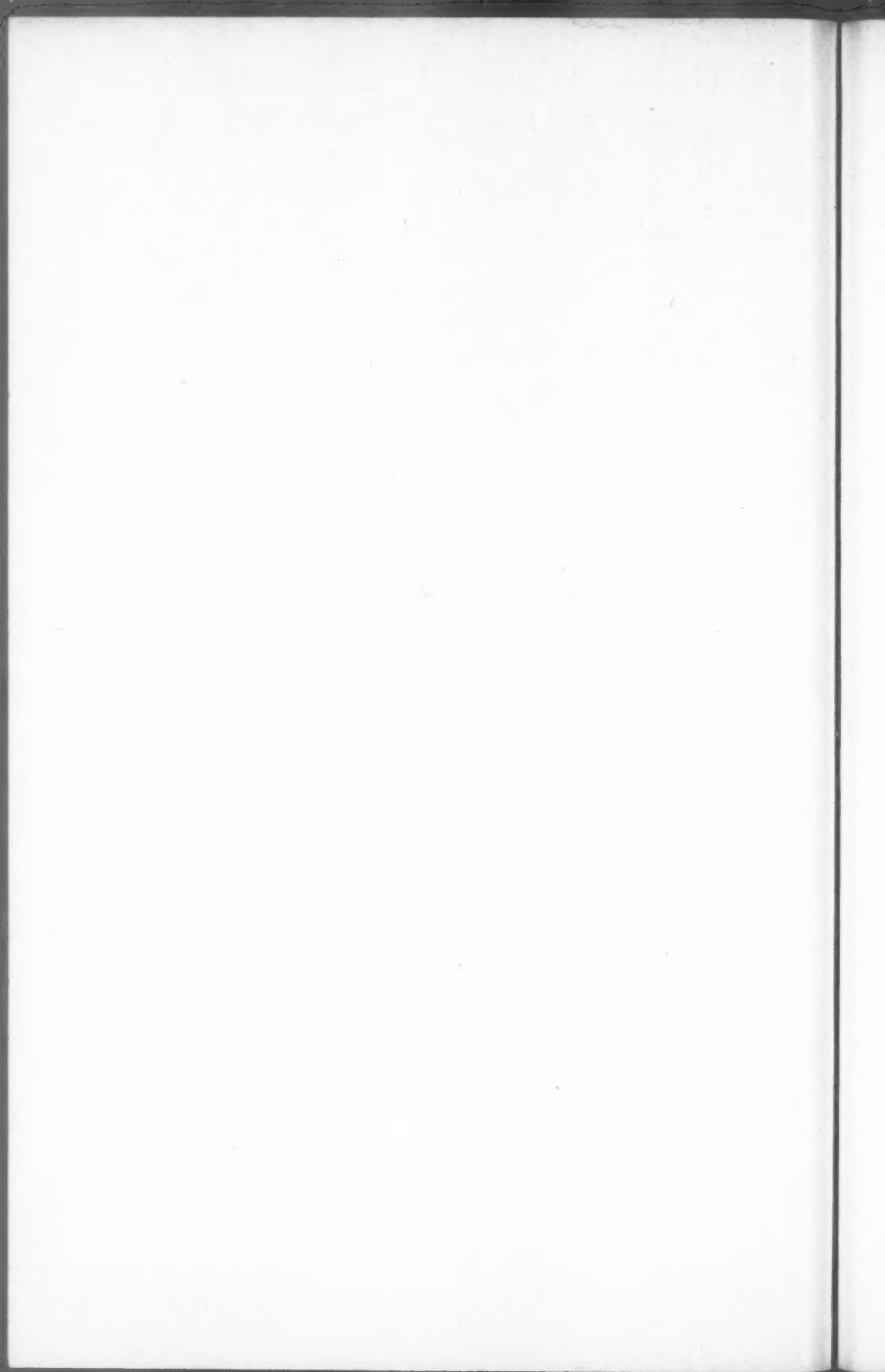
ECTOPIC SMOOTH MUSCLE IN THE HUMAN GASTRIC MUCOSA *

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In the course of routine and methodical histological study of large numbers of surgically removed stomachs, it became apparent that in a significant fraction of these there were definite abnormalities in the nonepithelial component of the mucous membrane, consisting of the presence of conspicuous bundles of smooth muscle in the lamina propria of the gastric mucosa, extending between its glands and occasionally compressing and distorting them. The accompanying photomicrographs show a few examples of the abnormalities referred to. The bundles of smooth muscle may be more or less conspicuous; however, in this study only those cases are included in which the mucosal architecture was definitely abnormal due to the presence of the ectopic muscle.

In some of our cases, formation of a new muscular membrane appeared to have occurred about midway between the muscularis mucosae and the free mucosal surface (Fig. 2). The gastric mucosa was thus divided into two zones: a more superficial one extending down approximately to the pit-neck junction; and a deeper one including the secretory portion of the glands. In other cases, there was a sort of plexiform arrangement of these abnormal muscular bundles, and the gastric glands enclosed in this meshwork could be mistaken for Brunner's glands because of their separation into small lobules circumscribed by the trabeculae of smooth muscle (Fig. 1). In still other cases—the most numerous—the abnormality manifested itself by the presence of scattered muscular bundles between the glands at varying distances from the muscularis mucosae and without a definite pattern. When a sufficient number of sections was taken, it was, in general, possible to establish that at some point there was a connection between the normal muscularis mucosae and the ectopic muscular bundles (Fig. 3).

In some stomachs the muscularis mucosae was dissociated into distinct bundles by the formation of lymphoid collections between them. These cases are not included in the present study.

For several years, it has been a routine practice in our laboratory to take sections of surgically resected stomachs following a standard pattern. By this method it is easy to orient the microscopical preparations in relation to the different regions of the organ. This practice made it possible to establish that, in the majority of the specimens

* Received for publication, July 1, 1946.

examined, the bundles of ectopic smooth muscle were situated in the antrum and in the pyloric canal, especially in those portions of the anterior and posterior gastric walls adjacent to the lesser curvature. It also has been my definite impression that these bundles of smooth muscle tended to radiate from the lesser curvature toward both gastric walls, while only exceptionally was their direction parallel to the axis of the lesser curvature.

Little can be found in the medical literature regarding the abnormality which is the subject of this paper. Normal histology teaches that in the mucous membrane of adult stomachs there may be found some individual smooth muscle fibers in the lamina propria, running between the glands and parallel to them. This seems to have little relationship to the findings that are studied here. More interesting is the fact that in the human embryo (Möllendorff,[1] page 113) the smooth muscle of the gastric mucosa begins to differentiate from the stroma of the lamina propria about the 15th week and, in these early stages, shows a very disorderly arrangement throughout the mucous membrane without the formation of a well differentiated muscularis mucosae. Of some interest are other facts from comparative anatomy, *i.e.*, that in some vertebrates, such as birds, reptiles, crocodiles, there is either no well differentiated muscularis mucosae and only irregularly scattered smooth muscle fibers between the glands, or, as in the glandular stomach of birds, there may be a duplication of the muscularis mucosae to form two parallel membranes between which there are portions of the gastric glands (Möllendorff [1]). In the series of human stomachs studied, there were specimens in which the arrangement of the smooth muscle in the mucosa suggested both of these types.

Only a few of the writers who have studied gastric lesions have made mention of these conspicuous bundles of smooth muscle. In the treatise of Henke and Lubarsch, Konjetzny [2] and Hauser [2] described the same abnormality that we are studying here, but interpreted it as a "neoformation" of smooth muscle and connective tissue as a part of a scarring process. Robertson,[3] in 1939, described a "hyperplasia of [the gastric] glands and disorganization of [the] muscularis mucosae" which, from his illustrations, appears to be the same condition here described. He considered it a result of the healing of superficial ulcers. Guiss and Stewart,[4] in their paper on chronic gastritis (1943), stated that "in the pyloric region smooth muscle extensions of the muscularis mucosae are normally found between the pyloric glands." This is "not a constant finding and as a criterion for a microscopic diagnosis of chronic atrophic gastritis it is probably not reliable."

Gitlitz and Colp,[5] in an excellent paper on "Gastric Histology and Subtotal Gastrectomy" (1943), described a proliferation of collageno-muscular tissue in the mucosa, usually accompanied by atrophy and disappearance of glandular elements. From their careful description, it is obvious that their findings are identical with mine. Their interpretation seems to be that these changes are the result of hyper-regeneration in the process of repair of mucosal ulcers.

As we have seen, a few authors have observed the presence of abnormal smooth muscle bundles in the human gastric mucosa. Some have regarded it as a sign of hyper-regeneration of the muscularis mucosae occurring as a part of the process of chronic gastritis or as a replacement of atrophic glands. Others have believed that it probably has no pathological significance and that it may represent a sort of individual variation within the limits of normal.

It is difficult to agree with the theory of regeneration of smooth muscle. Save a few and well known exceptions (pregnant uterus, new vessels in canalized thrombi), the normal smooth muscle is not known to proliferate or regenerate to any extent. In the stomach, I have never seen any sign of proliferation of smooth muscle fibers in association with erosions or ulcers of the gastric mucosa. These injuries of the smooth muscle have healed by fibrous tissue scars.

TABLE I

Partition of 100 Unselected, Surgically Removed Stomachs as to Diagnosis

Gastric ulcers	18
Duodenal ulcers	57
Jejunal ulcers	5
Carcinomas	23
Lymphosarcomas	2
Total	105
Less 5 cases of multiple gastroduodenal ulcers	5
	100

After having observed this abnormality in a considerable number of stomachs, an attempt was made to analyze our cases with the purpose of ascertaining a possible relationship between the histological findings and the clinical and radiological symptoms. With this in mind, I reviewed the anatomo-pathological, radiological, and clinical pictures of an unselected group, comprising a series of 100 examples of partial gastrectomy performed in the Surgical Department of the Presbyterian Hospital during a period of about 2 years. Table I presents these cases subdivided according to their respective diagnoses. In this group, 56 cases showed bundles of aberrant smooth muscle in the lamina propria. The distribution of this abnormality in this series is analyzed in Table II. When the respective percentages are analyzed, it becomes obvious that there is no significant correlation of this finding with any of the pathological conditions included in this series.

Table III is an attempt to compare the frequency of those radiological, clinical, and anatomo-pathological features that were considered of greatest significance in the cases having supernumerary smooth muscle in the gastric mucosa with their frequency in the cases in which this finding was not present. The incidence of the radiological features

. TABLE II

Relation of Ectopic Musculature to Diagnosis of 100 Resected Stomachs

Fifty-six examples of ectopic smooth muscle occurred with:

34 duodenal ulcers (59% of all duodenal ulcers)
8 gastric ulcers (44% of all gastric ulcers)
12 carcinomas (52% of all carcinomas)
2 marginal (jejunal) ulcers (40% of all marginal ulcers)

under consideration was not significantly different in the two groups. The average duration of the symptoms was somewhat higher in the first group. The only significant difference was that in the cases with bundles of supernumerary smooth muscle in the gastric mucosa the incidence of pyloric hypertrophy was more than twice that found in the other cases.*

TABLE III

Comparative Incidence of Other Findings in Stomachs
With and Without Ectopic Smooth Muscle

	Ectopic smooth muscle	
	Present	Absent
Delayed emptying of stomach (roentgenologically)	61%	50%
Exaggerated mucosal folds of antrum (roentgenologically)	50%	45%
Hypertrophy of pylorus	59%	27%
Average duration of symptoms	6.9 yrs.	4.4 yrs.

In conclusion, in a significant number of surgically resected stomachs, abnormal smooth muscle bundles can be found in the lamina propria. These can be compared with those in some animal species (reptiles) and perhaps in the human embryo. No mention of this muscle is found in any treatise of human histology and only rarely can it be found in papers dealing with chronic gastritis and with the pathology of the stomach in general. To my knowledge no satisfactory explanation has been offered.

Logically, it would seem that some significance must be attached to this feature because of its relative frequency. In this series, the only significant facts related to the presence of this muscle were a frequent

* The pyloric muscle was considered hypertrophied when its thickness, measured in the opened specimen, was 5 mm. or more.

hypertrophy of the pylorus and a longer duration of the symptoms of gastric disease.

As a tentative explanation, I believe that these findings may represent hypertrophy and perhaps hyperplasia of the normal rudimentary muscle of the lamina propria of the human gastric mucosa, perhaps directed towards increasing the formation of the longitudinal mucosal folds grossly described and studied by Forssell[6] and by him interpreted as directed toward facilitating the emptying of the fluid or semifluid contents of the stomach.

SUMMARY

In a considerable number of surgically resected stomachs, the mucosa of the antral pyloric region has shown an abnormality consisting of conspicuous bundles of smooth muscle extending between the glands and appearing to radiate from the lesser curvature toward both anterior and posterior gastric walls. An attempt is made to interpret this abnormality on the basis of the anatomo-pathological and clinical findings as hypertrophy and possibly hyperplasia, perhaps directed toward increasing the longitudinal mucosal folds.

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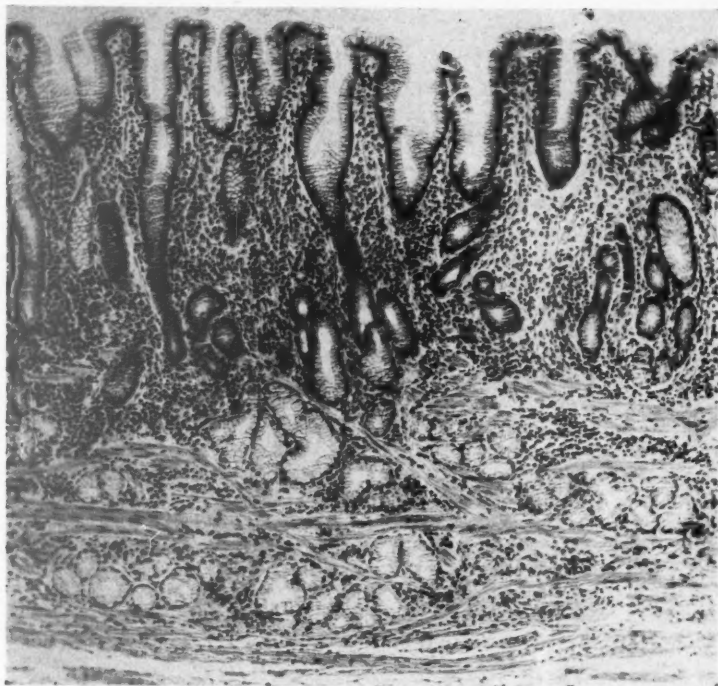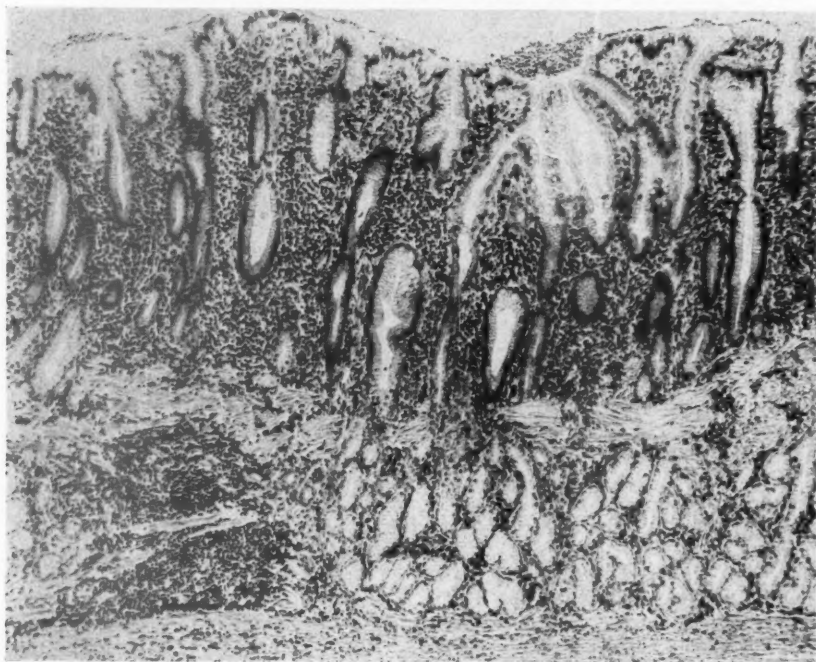
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 84

FIG. 1. Ectopic smooth muscle arranged in plexiform fashion, circumscribing groups of gastric antral glands.

FIG. 2. Ectopic bundles of smooth muscle which appear to form a second muscularis mucosae at the level of the pit-neck junction.
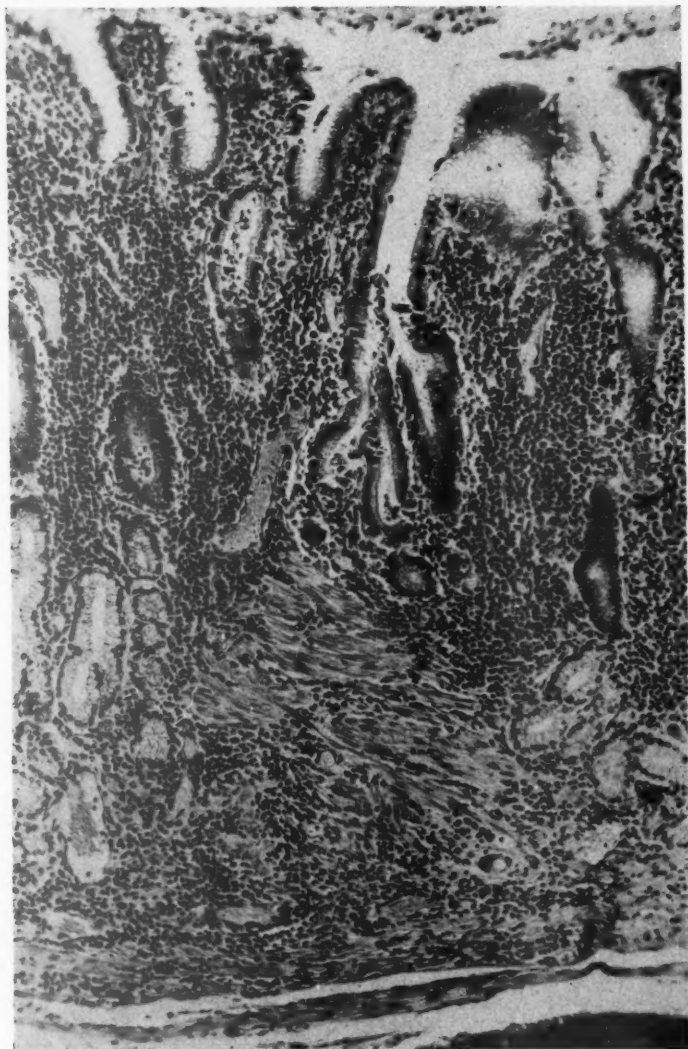
PLATE 85

FIG. 3. A conspicuous bundle of smooth muscle arising obliquely from the muscularis mucosae.

3

Lattes   Smooth Muscle in Gastric Mucosa

FIG. 4. Group of gastric antral glands completely surrounded by abundant ectopic smooth muscle.

4

Lattes   Smooth Muscle in Gastric Mucosa